TESTING CAUSAL HYPOTHESES AND ASSOCIATIONS BETWEEN PERINATAL RISK FACTORS AND OFFSPRING MORBIDITY AND MORTALITY

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This work is dedicated to my son and compass, Zephyr Lucas Anderson.

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The Developmental Origins of Health and Disease (DOHaD) hypothesis is a broad theoretical framework that highlights how early risk factors have a causal influence on later physical and psychopathological outcomes. Numerous studies have documented such associations and underlying mechanisms have been hypothesized. Most existing studies, however, have not been able to rule out the possibility of environmental and genetic confounding. Thus, concerns exist about causal interpretations of the statistical associations identified between early risk factors and later outcomes.

The six projects in my dissertation use quasi-experimental designs to rigorously test causal inferences across perinatal risk factors and offspring outcomes. The first two projects use a natural experiment approach to compare risk and hypothesized mechanisms across sensitive periods of development. In particular, the random occurrence of maternal bereavement stress across the preconception, prenatal, and postnatal periods was studied as a risk factor for offspring infant mortality and child and adult psychiatric problems. The next pair of projects examined birth weight and physical, psychiatric, educational, and socioeconomic problems using a sibling-comparison design. The final two projects used cousin-comparisons to explore the parental correlates and offspring psychiatric and education problems associated with interpregnancy interval, or the duration between the birth of an earlier born sibling and the conception of following sibling. Across these projects, findings both support and refute previous causal claims and important novel associations are identified.

These studies allowed for a thorough examination of the nature of the associations between several perinatal risk factors and offspring physical, psychiatric, educational, and socioeconomic problems. The projects illustrate how combining several quasi-experimental designs can specifically test the DOHaD hypothesis by ruling out plausible alternative hypotheses. My findings also inform the direction future DOHaD-based studies should pursue.

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1. INTRODUCTION

Complex interactions between genetics and the environment constantly and dynamically influence the course of development [1]. The perinatal period, the time prior to and immediately after childbirth, however, presents a particularly instrumental phase of development for the offspring [2-7]. The perinatal period is distinguished by a rapid rate of neuronal and physical development; unrivaled by any other point in life [5, 8]. Due to the rapid development, experiences during the perinatal period may initiate a cascade of effects that have lasting influence on the individual because of increased sensitivity or vulnerability to events or insults [7, 9]. These theories are at the core of the Developmental Origins of Health and Disease (DOHaD) hypothesis. The DOHaD hypothesis suggests that early life influences can causally impact later disease risk when the insult is experienced during the sensitive perinatal period [10-12].

The commonly held assumption that perinatal risks *cause* adverse outcomes, as presented in the DOHaD hypothesis [10, 13] has yet to be rigorously tested, however. Although numerous studies support the DOHaD hypothesis [10, 14, 15], the statistical associations may be due to unmeasured selection factors associated with the both the risks and outcomes [16]. Alternative explanations for the associations include genetic and environmental selection factors that influence the likelihood of experiencing both the risk and outcome [17, 18]. Drawing causal inferences, as well as determining precise and accurate estimates of the strength of the associations, is timely and essential for the field to efficiently move forward. These steps may clarify the etiology of numerous adverse outcomes and lead to the identification of causal mechanisms. Discovering modifiable causal risk factors is necessary for the creation of successful prevention efforts [19].

The current composition of six projects seeks to test causal assumptions in the DOHaD hypothesis and is uniquely prepared to do so. As part of this investigation, I examine the strength of previously found associations, as well as novel, theoretically driven, associations. I aimed to critically examine sensitive periods of perinatal development [2-5] while exploring potential mechanistic pathways linking perinatal risk factors with adverse offspring outcomes across the lifespan. To accomplish these goals, I use one of the most comprehensive, longitudinal population databases in the world, the Swedish population registers (N ≈ 3.6 million). Risk factors include important and universal measures of stress exposure, birth weight, and interpregnancy interval. The outcomes I study span a broad range of important indices of physical, psychiatric, educational, and social problems across infancy, childhood, and adulthood as well as mortality across the life span [13]. I use rigorous quasi-experimental approaches, or designs that utilize methodological and statistical means to test alternative explanations, to more precisely estimate if causal inferences can be drawn from the associations identified in the entire population [13, 17]. In particular, I utilize natural experiments and cousin- and sibling-comparison designs as methodological approaches to separate co-occurring genetic and environmental influences. Overall, the conclusions from the current set of studies are poised to provide critical information for determining the direction future studies based on the DOHaD hypothesis should pursue in order to continue to make meaningful advancements.

1.1 The Developmental Origins of Health and Disease (DOHaD) Hypothesis

Research on the associations between fetal experiences and adult outcomes was pioneered by Forsdahl [20] and later well established by Barker and colleagues [10]. Some of the first associations linking fetal development to adult health were reported between low birth

weight and the increased risk of developing cardiovascular disease and Type 2 diabetes mellitus [21-24]. The “thrifty phenotype” was used to describe how the association was believed to show that low birth weight infants channel their limited prenatal energy resources, or translate the “weather forecasts” of the ex utero environment [25], into essential organ development as opposed to growing large in body size and weight [26]. If the postnatal environment does not match the in utero conditions, then the postnatal low birth weight child would be maladapted to the ex utero conditions, leading to increased risk for metabolic dysfunction and cardiovascular disease as an adult [25, 27, 28]. The term “fetal programming” was once used to describe the hypothesis that the fetus adjusts its phenotype in utero as a means to be optimally adapted to the conditions of the postnatal environment [26]. Because “programming” implies a deterministic process [10], however, the term has fallen out of favor [26]. Instead, the “Developmental Origins of Health and Disease (DOHaD) hypothesis”, is now the framework for exploring associations between many perinatal risk factors and offspring outcomes [10, 11, 25, 27].

The DOHaD hypothesis may be considered a variation of the broader, normal biological phenomenon of developmental plasticity [13, 29]. Associations between early risk and later adverse offspring outcomes are either a result of (1) pathological dysregulation of normal homeostatic development, (2) a consequence of normal adaptation to a constrained environment resulting in suboptimal development, and/or (3) a consequence of an adaptive developmental response to a challenging environmental condition resulting in a trade-off, that although not ideal, successfully overcomes the demanding environment [11, 30]. It has also been hypothesized that what is “programmed” is the degree of postnatal plasticity [12]. These processes occur in response to an event during sensitive periods of development. Sensitive periods are time spans during development when plasticity or vulnerability is increased

corresponding to changing properties of neural circuitry [4, 5, 7]. Therefore, in a highly complex fashion [7], developmental timing of exposure to an insult is critically important in determining the consequence of the event.

Studies continue to use the DOHaD hypothesis framework to explore different risks and numerous offspring outcomes, often claiming causality [13]. Before determining which, if any of the above processes best describes the associations found, the assumption of causality between early risk and later outcome must be tested [10, 13, 16].

1.2 Perinatal Risk Factors

The current set of studies focuses on three perinatal risk factors: Maternal stress exposure, offspring birth weight, and interpregnancy interval. Details about the previous research performed on these risk factors are presented in the following sections. Other perinatal risk factors, such as smoking during pregnancy [31], young and old maternal age at child birth [32-34], and preterm birth [35-47] for example, are also highly correlated with adverse offspring outcomes across the life-span. The focus on maternal stress exposure, offspring birth weight, and interpregnancy interval is driven by several factors. First, there is a need to rigorously examine the causality between the associations found between maternal stress exposure, low birth weight, and interpregnancy interval and offspring outcomes. It is essential and timely to address this need because many researchers have assumed that previously identified associations are causal without properly testing causality in human populations [10, 13, 16]. If the associations are not causal, then intervention efforts aimed at reducing these particular risk factors may not lead to reduced adverse outcomes in the offspring. Second, stress, birth weight, and interpregnancy interval are all interrelated risk factors. For example, giving birth to a preterm or low birth

weight baby is associated with shorter interpregnancy intervals [48] and short interpregnancy intervals may increase prenatal maternal stress exposure [49]. Third, although they are related, each risk factor would act through different causal mechanisms if they are causally associated with offspring outcome. Thus, studying how this group of risk factors predict the same outcomes has the potential to shed light on disease-specific etiological mechanisms.

Fourth, although the field would almost always benefit from replication, some previous work using quasi-experimental designs in human populations has begun to address whether the associations between smoking during pregnancy [50-52], maternal age at child birth [53], and preterm birth can be considered causally connected with adverse offspring outcomes [54]. Fifth, the current projects will be conducted using the largest, most comprehensive population registries available, the Swedish population registries. While using these large databases is extremely beneficial, secondary data analysis in population registers also presents limitations for the risk factors that may be examined. For example, detailed information on maternal nutrition [23, 55, 56] in the perinatal period has not been recorded. These three risk factors, therefore, are indices that can be reliably and validly assessed in the registries. Finally, maternal stress exposure, offspring birth weight, and interpregnancy interval vary on their ability to be modified and the target of modification, mother, offspring, and family. In order to promote complete yet applicable information for intervention or prevention efforts, taking this multi-level approach may be most useful.

1.2.1 Maternal stress

Numerous previous studies have investigated maternal stress exposure as a risk factor for the developing offspring [for review see 14]. Researchers have asserted that precisely examining

developmental timing is of primary importance [7]. Preconception, prenatal, and postnatal maternal stress may each present unique environmental risk periods based on different causal mechanisms of association [6, 7]. The preconception, prenatal, and postnatal periods also each present unique opportunities to intervene and improve offspring outcomes [7].

In humans, preconception stress has been with increased risk for adverse birth outcomes [57], attention-deficit/hyperactivity disorder (ADHD) [58], and affective disorders [59] in male offspring. In rodents, preconception stress is associated with altered adult offspring memory functioning [60] and differences in affective and social behavior [61]. Prenatal maternal stress is associated with adverse birth outcomes [62, 63], ADHD and autism spectrum disorder [ASD; 64, 65], and schizophrenia [66], along with a multitude of other adverse outcomes [for review see 14]. Postnatal parental stress is associated with increased offspring ASD and Asperger syndrome-related impairment [67, 68], as well as ADHD [69]. Children exposed to postnatal neglect and abuse are also at greater risk for a host of psychological problems, such as affective disorders [70].

1.2.2 Offspring birth weight

Birth weight was the original risk factor examined by Barker [10, 21]. Birth weight is a proxy measure of fetal development and may be influenced through variety of mechanisms [71] including prenatal maternal stress exposure [72, 73] and interpregnancy interval [74]. Previous research has shown that up to 40% of offspring born very low birth weight (< 1500g) will not become fully functional and independent adults [75]. Low birth weight has been suggested to be associated with cardiovascular and metabolic mortality and morbidity [10, 21-24, 55, 76-81], white matter abnormalities [82], academic and behavioral problems [83-86], neuropsychiatric

disorders [42, 87-91], ASD [89, 92], and poor social outcomes [84, 93], although conflicting results across outcomes have been reported [84, 87, 94, 95]. Decades have passes without a rigorous examination of the causal assumptions between birth weight and these outcomes.

1.2.3 Interpregnancy interval

Interpregnancy interval is the duration between the birth of an older born sibling and the conception of the following sibling. Excessively short or long interpregnancy intervals, typically less than one year or more than three years, are considered perinatal risk factors for a variety of offspring physical and psychological outcomes [74, 96-99]. More specifically, short and long interpregnancy intervals are associated with increased risk for the offspring to be born preterm, low birth weight, and small for gestational age [74, 100-103]. Short and long interpregnancy interval increases the offspring's risk for stillbirth and infant mortality [104, 105]. Studies have also shown associations between short interpregnancy interval and childhood and adult psychopathology outcomes including increased risk for ASD [98] and schizophrenia [97, 99]. Some researchers, however, have rightly noted that these associations should not be assumed to be causal [58, 106] because of the numerous uncontrolled confounding factors in previous research [60, 104, 107-111]. Assuming causality between this particular risk factor and outcomes is compelling, however, because interpregnancy interval is a relatively modifiable risk factor [112].

1.3 Causal Inference

Although associations between perinatal risk factors and offspring development have been identified across populations using different sampling strategies and plausible mechanistic

hypotheses have been proposed, causal inferences cannot be drawn [13, 16]. This is because (1) direct research on pregnant women is necessarily limited due to ethical constraint, (2) generalization from animal research is limited, (3) traditional designs that compare unrelated individuals varying on the risk factor are replete with confounding factors.

1.3.1 Historical perspective on research on pregnant women and fetuses

Ethical and methodological issues make direct research on pregnant women and fetuses difficult [113]. Pregnant women and fetuses are currently considered vulnerable research subjects. To be considered "vulnerable", the population must present with a diminished capacity to provide informed consent because they have (1) a compromised decision-making capacity and/or (2) they lack the power or ability to act in their own interests [114, 115]. Although pregnant women are not objectively vulnerable according to these standards, fetuses are. Fetuses lack power and decision-making ability. Because the two are inseparable, it is current research practice to consider pregnant women and fetuses vulnerable whether the research question focuses on the woman or her fetus. Therefore, based on the principle of respect for persons set forth in The Belmont Report [116], there is an ethical imperative to protect these vulnerable populations from research exploitation or harm.

Historically, harm to pregnant women occurred because of exclusion from research studies rather than exploitation. Researchers were wary to include pregnant women, or women that could become pregnant, because of the liability and long-term risk inherent in this population [117]. Less than 20 years ago, the U.S. Food and Drug Administration (FDA) followed a drug research policy that excluded women "of childbearing potential" from participating in research studies [118]. While the exclusion was likely intended to protect the

vulnerable population, the action directly violated the pregnant woman's right to justice which states that the burden and benefits of research be equally shared among all persons [113, 116, 119]. One of the most egregious consequences of restricting the woman's right to justice was the thalidomide tragedy of the 1950s and 1960s which left tens of thousands of offspring severely malformed. The tragedy was due to a lack of testing thalidomide in pregnant women [120]. Overall, the historic ethical and practical difficulties of conducting research on pregnant women has limited our understanding on this crucial period of development.

Some changes have been made to research practices. For example, In 1993, the FDA reversed the research restrictions on women of childbearing potential based on the fact that the exclusion of women from clinical drug trials had resulted in a lack of scientific data concerning the risks and benefits of certain drugs to this population [118]. Additionally, the Common Rule in the Code of Federal Regulations (CFR) Title 45, Part 46, of the U.S. National Research Act now requires that research protocols include special protection for pregnant women [114]. Specifically, the regulation (45 CFR 46.204) allows for pregnant women or fetuses to participate in research if (1) there is only minimal risk to the fetus and the purpose of the research is to develop biomedical knowledge particularly important for pregnant or fetal populations, or (2) if the risk to the fetus is greater than minimal, but the research findings have the potential to directly benefit the woman, her fetus, or both parties [114]. In 1994, the Institute of Medicine issued a report recommending that pregnant women be "presumed eligible for participation in clinical studies" [121]. Many universities' Institutional Review Boards (IRB), however, still regard pregnancy as a primary cause for exclusion, even in studies that carry minimal risk [122, 123]. The ethical complexity and need for balance between protection of and experimentation for the benefit of pregnant women and fetuses, will keep research progressing cautiously.

1.3.2 Previous research design limitations

While the responsible conduct of research on perinatal populations has improved, true experimentation within the population will always remain necessarily limited. True experimentation involves random assignment to different study conditions. In large samples, the random assignment of participants to different experimental risk environments eliminates the possibility that the participant's genetic characteristics and experiences are systematically confounded with their experimental condition. Thus, with the assumption that covarying factors are equal across experimental conditions, researchers can infer that a particular experimental condition has a causal influence on the outcome if differential outcomes are observed between groups. Determining if causality exists is critically important because modification of a risk factor will only affect the outcome if the association is casual [19]. In the current set of projects, a true experiment might involve the random assignment of women to different conditions of interpregnancy interval length. This design is clearly untenable due to ethical and feasibility issues [124]. As a result, the overwhelming majority of human research on perinatal risk factors has relied on traditional epidemiological designs.

Traditional epidemiological designs compare outcomes across unrelated offspring with and without exposure to the studied risk factor [14]. While traditional designs are advantageous for several reasons (e.g. lower cost, relatively small sample sizes, data availability, etc.), inferring causality between risk factors and outcomes is problematic. Traditional designs are unable to control for unmeasured between-family characteristics that may be driving the investigated association [17, 125]. For example, perinatal risk factors are associated with numerous environmental risks that are themselves predictive of subsequent offspring difficulties [83]. In the case of perinatal maternal stress exposure, for instance, some individuals are more

likely to experience stressful life events [125], and thus, traditional designs may be confounded by nonrandom selection into high stress life conditions. Similarly, family and twin studies indicate that genetic factors influence birth weight and other perinatal risk factors [126, 127]. Genetic confounding due to gene-environment correlations could therefore account for the statistical associations between the risk and outcome. Even if numerous covariates are controlled for in the statistical models, it is impossible to rule out alternative explanations for associations between risk and outcome when using a traditional design [16, 128].

Animal models have begun to provide opportunities to determine if associations between perinatal risk and outcome are consistent with a causal explanation [129, 130]. Rodent and non-human primate studies with random assignment have shown that early under nutrition [131, 132] and physical and psychological stress [60, 61, 133, 134] are associated with several adverse outcomes, such as adverse birth outcomes, metabolic disorders, attention and motor disturbances, and impaired emotion regulation and memory functioning. Drawing conclusions from animal studies, however, is problematic. As compared with humans, non-human animals have substantially different reproductive systems, physiology, and developmental trajectory [8, 135, 136]. Animal research designs may also present significant differences in risk and outcome variables. For example, most animal studies on low birth weight involve maternal dietary manipulation which may or may not lead to low birth weight [137] and may or may not reflect the mechanism through which human fetuses are born low birth weight. Non-human primate studies more closely mirror the human brain structure and functioning, stress response, and developmental trajectory as compared with rodent studies; however, non-human primate research is difficult to conduct because of small sample sizes, high cost compared with rodent studies, and generalization to humans remains problematic [133, 135, 136, 138].

1.3.3 Quasi-experimental design alternatives

Given the restrictions of random assignment and problems of generalizing from animal models, researchers must rely on creative quasi-experimental designs to rule out competing explanations and determine causal inference in this population [139]. Quasi-experimental approaches utilize design features to account for possible confounding [140-142], including environmental selection factors [143], genetic selection factors (due to gene-environment correlations) [125, 144], and reciprocal influences or child effects [145]. Each type of quasi-experimental design has its own strengths and limitations [146]. Therefore, converging evidence from multiple studies and multiple designs is necessary to make strong causal inferences [142].

Prominent scholars have called for increased use of quasi-experimental studies of early causal risk factors because of the limitations inherent in the existing research [12, 17, 147, 148]. The quasi-experimental designs proposed in the current set of projects partially address the weaknesses inherent in traditional epidemiological studies by reducing potential threats to internal validity [149-151]. Research on perinatal risk factors have benefitted from the advancement of quasi-experimental research design by using natural experiments and within-family designs [147]. Natural experiments and within-family designs help to isolate risk from associated confounds and allow for the examination of timing of exposure to risk and sensitive periods [7]. Numerous other quasi-experimental designs exist, but are less well suited for the current research questions [151, 152]. For example, a twin-comparison may not be able to separate prenatal risk conferred to the offspring because most often both twins will have experienced the risk.

1.3.3.1 Natural experiments

A natural experiment benefits from variations in independent variables that are beyond the control of the participants. The natural variable or event utilized as a risk indicator must be clearly defined, time-limited, and generally accepted as an event that is beyond normal, daily life, or be structured in such a way that there is an exposed and unexposed control group [151]. Natural experiment designs of perinatal risk factors take advantage of the often random timing of natural events and compare women who experienced the event at different stages before, during, or immediately after their pregnancies to women who did not experience the stressor [153]. Natural experiments that have previously been used in perinatal research include exposure to famine [56], influenza outbreak [154], circumscribed war [155-159], earthquakes [160, 161], ice storms [162, 163], and death, illness, and hospitalization of a relative [164-166].

The natural experiment used in two of the current projects is random timing of exposure to an individual-level, objective stressor: death of a first degree relative of the mother. Defining stress as the date of death of a relative provides an exposure that results in substantial psychological stress [167] and allows for the examination of the role of timing of vulnerability via a natural experiment framework. Date of death of a first degree relative is also an accessible variable within large population databases and has been used previously [164-166].

Despite the high regard given to natural experimental designs [148], limitations and assumptions that must be considered. Natural experiments within large population databases do not allow for a complete picture of the "exposed" and "unexposed" groups to be formed. In the current study, this is important to note because there is variability in how individuals react to stressors, including the death of a family member [168, 169]. There may also be events that influence the outcome that go unmeasured. Although we cannot directly address these

drawbacks, results from the current research projects will help replicate or refute previous findings, establish novel associations, and get one step closer to causal inference by using one of the largest population-based samples with detailed assessments of mortality and morbidity.

1.3.3.2 Sibling-comparisons

To understand the mechanism through which a risk influences later outcomes, genetic and environmental transmission mechanisms must be pulled apart [17]. Fortunately, quasi-experimental methods, such as sibling-comparison designs, can control for possible selection factors and aide in the delineation of co-occurring genetic and environmental risk factors [170].

The sibling-comparison is a within-family comparison of siblings differentially exposed to a risk factor (e.g., the siblings differed in low birth weight status). The comparison of siblings within families rules out all unmeasured environmental risks that affect siblings similarly [17, 170]. The sibling-comparison design also controls for parental genetic factors that make siblings similar and influence both the risk and the offspring outcome. If an association between the risk and outcome is robust to the sibling-comparison analyses, the results are consistent with, although do not prove, a causal association. On the other hand, if there is no within-family association and siblings that vary on the risk factor have the same rates of psychopathology, the results suggest that confounding factors account for the association between risk and outcome. Overall, the increased control over genetic and shared environmental confounds gained by utilizing a sibling-comparison design provides a rigorous alternative to traditional methods by ruling out alternative (e.g., third variable) explanations for the associations found.

Further specifying the sibling comparison design by examining both full- and half-siblings can also help to more precisely elucidate the underlying mechanisms through which the

early risk factor operates. Differences in the candidate risk exposure between half-siblings could be confounded by differences in the unshared parent's genes or differences in experiences provided by the unshared parent [17, 170, 171]. Thus, an alternative to the causal hypothesis is that the unshared parent's influences are confounded with the candidate causal environmental risk and that the association between risk and outcome is due to the unshared biological parent's genetic or environmental influence. If full- and half-sibling analyses yield the same results, this alternative hypothesis is not supported. Thus, while full-sibling comparisons rule out shared genetic factors from both the father and mother, analyses of maternal half-siblings (i.e., siblings that share a mother but not a father) provide insight into the possible importance of paternal effects [170]. By extension, one can see how testing sibling pairs of varying genetic relatedness (e.g., dizygotic and monozygotic twins) could also be used to gain traction on identifying causal influences [17].

Sibling-comparison designs also have limitations that must be considered. First, use of the design, requires large sample sizes to precisely estimate the various within-family estimates [172]. Fortunately, the current project addresses this challenge by using one of the largest, most complete, Swedish population-based sample of over 3.6 million individuals. Despite this, sibling-comparison analyses may not have enough statistical power to precisely estimate the magnitude of associations between rare risks and rare outcomes, such as stress during a particular trimester and schizophrenia. Second, associations may not generalize to individuals that do not have siblings [170, 173]. To test this limitation, we will run sensitivity tests to examine if family size moderates the associations found in the population and compare associations across cousins. Third, the Stable Unit Treatment Value Assumption (SUTVA) is the assumption that the effect of exposure to a risk factor (e.g., birth weight) is specific to each

participant (i.e., sibling) [152, 174]. To insure that carry-over effects do not influence subsequent pregnancies, we will statistically control for birth order may use other models (i.e., bidirectional case-cross over models [175]) to examine birth order effects [170, 173]. Fourth, definitive causal interpretations are not possible with a sibling-comparison design because it does not use random assignment and therefore, there still may be unmeasured variables that differ between siblings that causally influence the outcome [142, 176]. The only environmental factors not ruled out by sibling-comparisons, however, are those that (1) vary among siblings, (2) are correlated with the putative risk factor (i.e., maternal stress exposure, low birth weight, or interpregnancy interval) within the family, and (3) are correlated with the outcome variable [170]. Fifth, when the risk factors are not associated with the outcomes, sibling-comparisons cannot determine the source of confounding [170, 174]. If sibling-comparisons suggest that shared familial selection factors account for an association, subsequent studies can use other quasi-experimental designs to explore risk factors that are shared by siblings. Sixth, the treatment of measurement error during within-family analyses may artificially reduce the associations found [177], however previous studies support the high measurement quality of the risk factors used in the current set of projects [178].

1.3.3.3 Cousin-comparisons

Cousin-comparisons account for fewer confounds than sibling-comparisons, as cousins are less genetically (12.5% versus 50%) and less environmentally similar than siblings. Cousins, however, still share more genetic and environmental factors than random, unrelated individuals. Therefore, utilizing first cousins in analyses can help to draw conclusions about the causal and confounding processes that account for the associations between perinatal risks and offspring

outcomes [179]. For example, cousin-comparisons can be used to explore risk factors that may be confounded by birth order, such as interpregnancy interval. Cousin comparisons can also be utilized when carry-over effects may be possible. Thus, cousin-comparisons address many of the alternative explanations that sibling-comparisons leave partially open while still providing important advancements over traditional designs.

1.3.3.4 The importance of combining designs

Inherent limitations in each quasi-experimental design requires converging evidence from multiple designs to draw concrete conclusions [133, 140, 142, 146, 147, 179]. Combining several methodological approaches is necessary to pull apart co-occurring risks and provide a more nuanced understanding of the associations. Using multiple approaches also allows for critical assumptions and limitations in each design to be tested. For example, when combining findings across sibling- and cousin-comparisons, results can test if the assumptions of these designs have been met while also furthering the understanding of the mechanism driving the association. Using advanced quasi-experimental methods is a critical step in understanding the causal risk mechanisms of how early environmental and genetic factors influence important outcomes. Additionally, findings have the potential to provide the insight for future targeted epigenetic or gene-environment interaction research that will further clarify the etiology of numerous physical, psychiatric, and social outcomes.

1.4 Swedish Data Registers

In order to achieve the rigorous scientific, statistical, and methodological goals in the current set of projects, I use a large, population-based, genetically-informed sample from

Sweden. A large sample is necessary to have enough individuals that are differentially exposed to the risk, as well as enough cases of rare outcomes (e.g. infant mortality, schizophrenia) to have the statistical power to properly model the associations. Because the sample is reduced when limited to siblings and cousins, large and genetically informed samples are needed to precisely estimate associations [151]. Additionally, utilizing secondary data imposes no additional risk to pregnant women or fetuses and is therefore invaluable for research on these vulnerable populations [119]. The databases have detailed and validated diagnostic information on rare, well defined psychiatric and medical outcomes. We also have the ability to examine academic and social outcomes as well as mortality across the life span.

Use of a population database also presents limitations, however. We do not have control over the manner in which measures were assessed and most psychopathological outcomes are from inpatient care. Because the data only include individuals residing in Sweden, results may also have limited generalizability to other nations. Particularly relevant to the current study, Sweden boasts an unmatched prenatal care system and maternity/paternity leave allowance, which may act as protection against adverse effects of stress during pregnancy, reduce the likelihood of low birth weight, and influence interpregnancy interval length. The “unrelated” comparison group will include extended family members and when using multiple members of one family, the observations are not completely independent. The use of multilevel analyses in the unadjusted and adjusted models that explicitly accounts for the non-independence of the observations will be utilized to reduce bias in standard errors [180].

A combination of several Swedish population databases will be used across projects. Because the current project focuses on perinatal risk factors, the dataset will, at maximum, be

limited to individuals born in Sweden from 1973-2009, the period in which the highest quality data regarding the perinatal period are available (N≈3.6 million). I use the following registers:

1. *The Medical Birth Register,* kept by the National Board of Health and Welfare, contains the mandatory reporting information on all pregnancy outcomes and complications in Sweden from 1973 onwards, approximately 100,000 yearly. It includes data on more than 99% of all births [178, 181]. Information is gathered throughout the pregnancy and delivery using standardized records and includes pregnancy and delivery complications and offspring birth outcomes. The register also includes detailed demographic information, including maternal age at birth, maternal living situation, and parity.
2. *The Multi-Generation Register,* held by Statistics Sweden, contains information about biological and adoptive relationships for more than 11 million individuals living in Sweden since 1933 [182]. The Multi-generation register connects each person born in Sweden (since 1933) or ever registered as living in Sweden (1960 or later), to their biological and adoptive (if appropriate) parents. For each individual, the Multi-generation register includes an identification number that may be linked with offspring and parents.
3. *The Cause of Death Register,* kept by the National Board of Health and Welfare, contains date of death and principal and contributing causes of all deaths since 1958.
4. *The Migration Register,* held by Statistics Sweden, provides information on dates for migration in or out of Sweden.

5. *The National Patient Register*, contains discharge date, the primary discharge diagnosis, and up to seven secondary diagnoses assigned by the treating medical doctor according to the International Classification of Diseases (ICD) revisions 8 (until 1986), 9 (1987-1996) and 10 (from 1997) [183] since 1973 for inpatient hospital visits. Since 2001, this registry also includes outpatient medical treatment with ICD classification codes [184, 185]. With a Swedish population of about 9.2 million, this is largest national hospital register in the world.

7. *The National Crime Register* this registry provides information on all criminal convictions on those aged 15 (the age of criminal responsibility) and older since 1973 [186].

8. *The Education Register,* held by Statistics Sweden, contains mandatory reported information on the highest level of completed formal education gathered primarily from the continuously updated registers of graduates from compulsory, high school, and higher levels of education [187].

9. *The National School Register* includes grades in all subjects at the end of grade nine (at 16 years old) since 1983 [188].

10. *The Integrated Database for Labour Market Research (LISA)* includes information on all individuals registered in Sweden that are at least 16 years old as of December 31 for each year since 1990. The database integrates existing annual data from the labor market, educational, and social sectors [189] to provide assessments of family income, marital status, unemployment status, social welfare status, disability pension, sick leave status, education, and number of residential moves.

The individual is the primary index person in the LISA database, but connections to families and neighborhoods are also available.

1.5 Comprehensive Aims

All studies received approval by the Institutional Review Boards at Indiana University and the Swedish Karolinska Institutet (study approval numbers 1105005324 and 0911000810). The first two studies use a natural experiment design benefitting from the random timing of exposure to maternal stress across the preconception, prenatal, and postnatal maternal stress to predict (1) infant mortality and adverse birth outcomes and (2) offspring ASD, ADHD, non-affective psychosis, bipolar disorder, attempted suicide, and completed suicide using logistic regression and Cox proportional survival analysis. The next set of studies focus on the ramifications of impaired fetal development as indicated by low birth weight. More specifically, I use logistic and Cox proportional survival analysis to investigate the strength of associations between low birth weight and offspring mortality and physical, psychiatric, social, and educational morbidity. In these projects, I use a sibling-comparison design to test causal inferences by ruling out plausible alternative explanations. The final two studies explore interpregnancy interval. I first examine the associations between interpregnancy interval and adverse birth outcomes while exploring a variety of parental correlated. Then, I examine the strength of association between interpregnancy interval and childhood and adult psychiatric and educational problems.

By utilizing the Swedish population registries and advanced statistical and methodological techniques, the current six studies are positioned to make unparalleled contributions to the field. These studies aim to examine the causal inferences assumed in the

broad theoretical framework of the DOHaD hypothesis. Separately, the projects seek to explore new hypotheses, rigorously test established hypotheses, and use the most comprehensive data and advanced statistical methodology to move the field forward while scientifically investigating vulnerable populations. Together, the projects will paint a picture of offspring vulnerability, clarify outcome-specific vulnerability that may contribute to improved etiological understanding of important outcomes, and deepen the field's knowledge of early development and developmental psychopathology. In a field where testing causal associations is difficult, the findings will have important implications for future researchers; Our findings identify novel associations (i.e., increased risk of infant mortality associated with preconception maternal stress exposure), support established connections (e.g., the link between impaired fetal growth and offspring physical problems), and oppose other suggested causal associations (e.g., increased risk for autism following short interpregnancy intervals).

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2. STUDIES

2.1 Maternal Stress and Infant Mortality: The Importance of the Preconception Period

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Abstract

Although preconception and prenatal maternal stress are associated with adverse outcomes in birth and childhood, their relation to infant mortality remains uncertain. We used logistic regression to study infant mortality risk following maternal stress within a population-based sample of infants born in Sweden between 1973 and 2008 (N = 3,055,361). Preconception (6–0 months before conception) and prenatal (between conception and birth) stress were defined as death of a first-degree relative of the mother. A total of 20,651 offspring were exposed to preconception stress, 26,731 offspring were exposed to prenatal stress, and 8,398 cases of infant mortality were identified. Preconception stress increased the risk of infant mortality independently of measured covariates, and this association was timing specific and robust across low-risk groups. Prenatal stress did not increase risk of infant mortality. These results suggest that the period immediately before conception may be a sensitive developmental period with ramifications for infant mortality risk.

Keywords: preconception, prenatal, maternal stress, bereavement, infant mortality, infant development, stress reactions, health

Infant mortality, or death in the 1st year of postnatal life, places substantial stress on families and imposes a financial burden on society [1]. Despite substantial reductions in rates of infant mortality over recent decades, the rate is estimated at 6 to 7 deaths per 1,000 live births in the United States and, unfortunately, has remained stable for more than a decade [1]. Rates of infant mortality vary by maternal socioeconomic status and ethnicity and across nations [2]. Sweden experiences 2.7 deaths per 1,000 live births, whereas Afghanistan reports the highest rate of infant mortality worldwide, a distressing 121.6 deaths per 1,000 live births [3]. Identifying robust risk factors, vulnerable periods of development, and etiological mechanisms of infant mortality is essential for designing effective global prevention programs [4].

Research on the roles of preconception stress and prenatal maternal stress on infant mortality has been limited. Intervention research, however, has suggested that both preconception and prenatal stress may influence infant mortality [5, 6]. Poor preconception maternal mental health is associated with increased risk of having a stillbirth or a low-birth-weight child [7]. Preconception multivitamin use [6] and improved preconception self-care, characterized in part by reduced stress [5], are associated with reduced risk of adverse birth outcomes, such as preterm birth and small-for-gestational-age (SGA) status, which are among the strongest predictors of infant mortality [1]. Animal research has indicated that preconception stress is associated with long-term impairment in offsprings' brain functioning and plasticity [8]. Prenatal maternal stress increases the risk for adverse birth outcomes [9, 10] and stillbirth [11]. Thus, preconception and prenatal maternal stress may directly or indirectly (through adverse birth outcomes) increase offsprings' risk for infant mortality.

Exploring whether vulnerability differs by stress-exposure period may help to clarify sensitive developmental periods [12] and thereby improve our understanding of etiological

mechanisms of infant mortality. Preconception stress may affect the mother for several months [13] and, therefore, affect fetal development during conception and the vulnerable process of organogenesis. The prenatal period may be a period of increased sensitivity because of the rapid development of essential systems [14].

We sought to rigorously examine the potential associations between preconception and prenatal maternal stress and infant mortality in a large Swedish population. We hypothesized that exposure to both preconception and prenatal maternal stress would moderately increase infant mortality risk and that associations would be mediated partially by gestational age and SGA status [15].

Methods

Study population

After approval by the institutional review boards at Indiana University and the Karolinska Institutet, we constructed a large, population-based Swedish sample by linking several population registries. The Medical Birth Registry [16] included data on more than 99% of all births in Sweden between 1973 and 2009 and was used to obtain information on gestational age at birth and SGA status. Information on family relatedness was drawn from the Multi-Generation Registry [17]. The Cause of Death Registry was used to identify cases of infant mortality and family members' dates of death to indicate exposure to stress. The Education Register [18] provided data on parents' highest level of completed formal education, and the National Crime Register provided data on parental criminal convictions.

The initial sample comprised 3,632,650 individuals born between 1973 and 2008 whose data included their mother's identity. The offspring year of birth was truncated at 2008 to allow

all offspring to have the potential to live through the risk period. We removed offspring whose grandmother (*n* = 416,927; 11.5%) or father (*n* = 35,408; 1.0%) could not be identified. We excluded cases of multiple births (*n* = 75,777; 2.1%) because the rate of adverse birth outcomes for multiple births differs from that for singleton births [1]. We also excluded children with missing data on gestational age at birth (6,466; 0.2%), which was required for calculating the date of conception and determining risk-exposure windows. Offspring with a gestational age of more than 42 weeks and 6 days (*n* = 36,497; 1.0%) were removed. We also removed families with more than 13 children (54 families; < 0.1%) and one case (< 0.1%) for which parity information was missing. We then excluded offspring whose parental nationality status was unknown (*n* = 2,623; < 0.1%) and offspring who had immigrated to Sweden with their families before their 1st birthday (*n* = 3,536; 0.1%). The final cohort consisted of 3,055,361 (84.1%) infants who were still residing in Sweden at their 1st birthday.

Measures

The preconception period was defined as the 6 months prior to conception. The prenatal period was defined as the period between conception and birth. Preconception was further divided into two periods (6–4 months prior to birth and 3–0 months prior to birth). Similarly, the prenatal period was divided into trimesters (Trimester 1: 0–12 weeks; Trimester 2: 13–24 weeks; Trimester 3: 25 weeks to birth).

Preconception and prenatal maternal stress were defined as death of a first-degree relative of the mother. For preconception stress, first-degree relatives included parents, siblings, and already-born children of the mother. For prenatal stress, first-degree relatives also included the biological fathers of offspring. If more than one of a mother's relatives died within one exposure period, the first date of exposure was used. Offspring of mothers who experienced both

preconception and prenatal stress were removed from analyses (n = 204; < 0.01%). (No cases of infant mortality were identified within this subsample; therefore, sensitivity analyses could not be performed using this group.)

All models predicted a dichotomous indicator of infant mortality defined as death of the offspring within the 1st year of life. Preterm birth was defined as birth at or before 37 weeks of gestation. SGA status was indicated by birth weight less than 2 standard deviations below the mean for gestational age according to standard curves for the Swedish population [19].

Analyses

We used PROC SURVEYLOGISTIC in SAS 9.2 to obtain odds ratios (ORs) from logistic regression analyses that accounted for family clustering at the maternal level. The first model was unadjusted. The second model controlled for measured statistical covariates associated with stress exposure, infant mortality, or both [1]. Covariates included offspring birth year, sex, and birth order (first born, referent; second born; third born; or fourth born and later); maternal and paternal age (< 20 years; 20–24 years; 25–29 years, referent; 30–34 years; or > 34 years); highest level of maternal and paternal education (missing; primary or lower secondary education of 9 years or fewer; 1–3 years of upper secondary school, referent; or postsecondary education); parental country of birth (binary and categorized as Swedish or non-Swedish); and maternal and paternal lifetime history of criminality (binary). Analyses also were adjusted for previous infant mortality in the family, defined as the death of an already-born sibling outside of the pregestational or prenatal exposure window, because previous infant mortality may predict future conception outcomes and infant death [20].

To evaluate possible mediation by gestational age and reduced fetal growth, we examined whether preconception and prenatal stress predicted preterm birth and SGA status [10]. We

separately examined whether preterm birth and SGA status were associated with infant mortality [1, 15]. To test for mediation, we predicted infant mortality from stress exposure while adjusting for gestational age at delivery (22–27 weeks, 6 days; 28–30 weeks, 6 days; 31–33 weeks, 6 days; 34–36 weeks, 6 days; or 37–42 weeks, 6 days, referent) and SGA status.

Sensitivity analyses

Sensitivity analyses were used to rule out alternative hypotheses for the associations found. First, we examined moderation by offspring sex [1]. Second, risk for infant mortality following maternal stress in preconception months 18 to 13 and 12 to 7 was examined to test whether stress in preconception months 6 to 0 conferred a unique risk to the offspring. Third, we explored whether associations were present in offspring without adverse birth outcomes, restricting the cohort to offspring that were born full term, had a normal birth weight (≥ 2,500 g), and were not SGA. Fourth, in cases of offspring with siblings, we restricted analyses to include only those from sibling pairs with an average interpregnancy-interval length (12–35 months from birth of an older sibling to conception of the index offspring). Fifth, we limited the sample to offspring exposed to stress due to death of a maternal parent or sibling only, not an already-born child. Thus, we tested whether associations were independent of immediate-family mortality risk or due to cascading stress from a previous child's death. Finally, we restricted the sample to offspring for whom information on maternal smoking during pregnancy was available (birth years 1982–2008).

Results

We identified 8,398 (0.3%) infant deaths. Table 1 provides descriptive characteristics by stress-exposure status. As presented in Table 2, preconception stress predicted infant mortality in

unadjusted analyses (OR = 1.65, 95% confidence interval, CI [1.34, 2.02]), and the association remained robust to the inclusion of measured covariates (adjusted OR = 1.53; 95% CI = [1.25, 1.88]).

Preconception stress increased risk for preterm birth (adjusted OR = 1.19; 95% CI [1.12, 1.26]) and SGA status (adjusted OR = 1.14; 95% CI = [1.05, 1.23]). Preterm birth (adjusted OR = 16.05; 95% CI = [15.35, 16.77]) and SGA (adjusted OR = 9.04; 95% CI = [8.55, 9.56]) were associated with increased risk for infant mortality. Therefore, we further adjusted for gestational age and SGA status to study their potential mediating effects. The association with preconception stress remained robust (adjusted OR = 1.37; 95% CI = [1.11, 1.70]; see Table 2). Nevertheless, the reduction in magnitude (i.e., OR = 1.53 vs. OR = 1.37) suggests that shorter gestational length and SGA status partially mediated the association between preconception stress and infant mortality.

Prenatal maternal stress was not associated with infant mortality in unadjusted models (OR = 1.10, 95% CI [0.89, 1.37]), adjusted (OR = 1.05; 95% CI = [0.84, 1.30]), or models adjusted for birth outcomes (OR = 1.11; 95% CI = [0.88, 1.39]; see Table 2). We did not find large or statistically significant associations when we separated the prenatal period by trimester. We did, however, find associations between prenatal stress and increased risk for preterm birth (Trimester 2 adjusted OR = 1.16; 95% CI = [1.05, 1.27]) and between prenatal stress and SGA status (Trimester 2 adjusted OR = 1.19; 95% CI = [1.05, 1.34]).

As Table 3 presents, preconception sensitivity analyses revealed an interaction of mortality with sex, $b = -0.45$, $SE = 0.22$, $p = .04$, wherein male offspring were at a greater risk for infant mortality (adjusted OR = 1.83, 95% CI [1.42, 2.35]) compared with female offspring (adjusted OR = 1.15; 95% CI = [0.81, 1.64]). Stress exposure during preconception months 18 to

13 (adjusted OR = 0.91; 95% CI = [0.68, 1.22]) and preconception months 12 to 7 (adjusted OR = 0.97; 95% CI = [0.76, 1.26]) did not increase risk for infant mortality (Figure 1). Risk for infant mortality remained elevated in infants born at full term who were at normal birth weight and normal weight for gestational age (adjusted OR = 1.61; 95% CI = [1.20, 2.17]). The association was robust in offspring born within an average (12–35 month) interpregnancy interval (adjusted OR = 2.09; 95% CI = [1.37, 3.21]) and when stress restricted defined as the death of a maternal parent or maternal sibling only (adjusted OR = 1.31; 95% CI = [1.01, 1.69]). Finally, preconception stress continued to independently predict infant mortality when we controlled for smoking during pregnancy (adjusted OR = 1.35; 95% CI = [1.01, 1.81].

Discussion

Using Swedish population data, we found a novel and robust association between preconception maternal stress and risk for infant mortality. Preconception stress also predicted increased risk for preterm birth and SGA status [6, 10], and these adverse birth outcomes partially mediated the association between preconception stress and infant mortality. We did not identify associations between prenatal stress and infant mortality. These counterintuitive findings may be explained by an examination of potential mechanisms and future exploration of cause of death. Little is known, however, about potential mechanisms that may act during the preconception period. The mediating role of gestational age and SGA status suggests that preconception nutritional depletion may play a role in the association between preconception stress and infant mortality [5, 6]. Congenital malformations and sudden infant death syndrome (SIDS), both of which are leading causes of infant mortality [1, 15], may be more strongly influenced by preconception and early prenatal insults than by events later in pregnancy [21].

SIDS may be associated with brainstem-based control of autonomic functioning of breathing [22] through the serotonergic and noradrenergic neuronal systems [23], which develop early in organogenesis.

Stress due to bereavement following the death of a loved one affects the survivor's psychological, cognitive, behavioral, endocrine, physiological-somatic, and immunological characteristics and can do so for months after the death [13]. Etiological epigenetic mechanisms also may translate the effects of maternal preconception stress to the future fetus by affecting nutritional or hormonal maternal systems [5, 6, 24] and thereby affecting the mother's preparedness for pregnancy and affecting the fetus during the vulnerable period of organogenesis [25-27].

Sensitivity analyses suggested that male offspring were at greater risk for infant mortality than were female offspring [1, 28], although statistical power may have affected our ability to detect a similar association in females. A male-specific mechanism affecting the likelihood of SIDS has been identified and may act during early organogenesis [23]. The risk associated with preconception stress remained elevated in offspring of mothers with an average interpregnancy interval (12–35 months), which is notable because both short [29] and long [30] interpregnancy intervals are associated with infant mortality. The association also was present when we included only mothers who had experienced the death of a parent or maternal sibling only [31], which helps to rule out alternative explanations involving factors such as family mortality risk or cascading stressors from a previous child's death. The association also appeared to be specific to the period just before conception (see Figure 1).

Our sample was large (covering births over a span of 35 years), and we controlled for a breadth of statistical covariates and used a precise and reasonably random indicator of stress

[32]. Despite these strengths, future research must take additional methodological and statistical efforts to account for possible selection factors that contribute to both infant mortality and preconception stress exposure [32]. The death of a relative causes stress with a level of intensity that varies by individual and situation. It is possible that the death of a first-degree relative did not induce substantial stress in all mothers and that, in cases of death due to a long-term illness, it may have provided relief [33]. In addition, mothers might have experienced unmeasured stressors. Future research would benefit from considering the specific causes of death in infancy. In agreement with findings from clinical intervention studies [5], the results reported here suggest that preconception care is essential; maternal preconception stress increases the risk for infant mortality and adverse birth outcomes in offspring. Prenatal maternal stress, however, does not appear to influence risk for infant mortality. Our findings suggest that the 6 months immediately prior to preconception may be a sensitive developmental period with ramifications for the likelihood of offspring infant mortality. Longitudinal studies of women experiencing severe stress before conception might provide important knowledge about the mechanisms of infant mortality.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Table 1. Descriptive Characteristics of All Singleton Pregnancies in Sweden (1973–2008) With Live-Born Offspring by Maternal Stress Exposure Status

Characteristic	Stress exposure period		
	None (n = 3,007,775)	Preconception (n = 20,651)	Prenatal (n = 26,731)
Infant mortality	8,224 (97.93%)	93 (1.11%)	81 (0.96%)
Female offspring	1,461,754 (48.60%)	10,136 (49.08%)	13,003 (48.64%)
Birth order			
First[a]	1,292,084 (42.96%)	5,700 (27.60%)	9,229 (34.53%)
Second	1,113,150 (37.01%)	8,038 (38.89%)	9,922 (37.12%)
Third	439,833 (14.62%)	4,648 (22.51%)	5,139 (19.22%)
Fourth or higher	162,708 (5.41%)	2,265 (10.97%)	2,441 (9.13%)
Mother's age (years)			
< 20	97,026 (3.23%)	384 (1.86%)	535 (2.00%)
20–24	638,580 (21.23%)	3,175 (15.37%)	3,677 (13.76%)
25–29[a]	1,088,312 (36.18%)	6,495 (31.45%)	8,113 (30.35%)
30–34	821,248 (27.30%)	6,425 (31.11%)	8,481 (31.73%)
> 34	362,609 (12.06%)	4,172 (20.20%)	5,925 (22.17%)
Father's age (years)			
< 20	22,584 (0.75%)	94 (0.46%)	128 (0.48%)
20–24	342,691 (11.39%)	1,690 (8.18%)	2,024 (7.57%)
25–29[a]	949,940 (31.58%)	5,379 (26.05%)	6,596 (24.68%)
30–34	969,045 (32.22%)	6,778 (32.82%)	8,601 (32.18%)
> 34	723,515 (24.05%)	6,710 (32.49%)	9,382 (35.10%)
Mother's highest education			
Missing	5,037 (0.17%)	23 (0.11%)	38 (0.14%)
≤ 9 years	352,860 (11.73%)	2,960 (14.22%)	3,802 (14.22%)
1–3 years upper secondary[a]	1,492,808 (49.63%)	10,195 (49.37%)	13,086 (48.95%)
Postsecondary	1,157,070 (38.47%)	7,473 (36.19%)	9,805 (36.68%)
Father's highest education			
Missing	16,425 (0.55%)	115 (0.56%)	277 (1.04%)
≤ 9 years	563,504 (18.73%)	4,280 (20.73%)	5,603 (20.96%)
1–3 years upper secondary[a]	1,500,474 (49.89%)	10,107 (48.94%)	12,903 (48.27%)
Postsecondary	927,372 (30.83%)	6,149 (29.78%)	7,948 (29.73%)
Parental nationality			
Mother	2,879,452 (95.73%)	19,932 (96.52%)	25,841 (96.67%)
Father	2,751,560 (91.48%)	18,925 (91.64%)	24,442 (91.44%)
Criminal history			
Mother	330,389 (10.98%)	2,536 (12.28%)	3,396 (12.70%)
Father	1,137,853 (37.83%)	7,932 (38.41%)	10,385 (38.85%)

Note: The table presents numbers of infants, with percentages in parentheses, for each characteristic. Preconception stress exposure was defined as death of the mother's parent, sibling, or already born child. Prenatal stress exposure also included death of the father of the offspring. [a]Reference.

Table 2. Risk for Infant Mortality Across the Preconception and Prenatal Stress Exposure Periods

Stress exposure period	Offspring with stress exposure who died as infants (*n*)	Odds ratio		
		Unadjusted	Adjusted[b]	Adjusted for birth outcomes[c]
Preconception	93	1.65 [1.34, 2.02]	1.53 [1.25, 1.88]	1.37 [1.11, 1.70]
6–4 months preconception	50	1.75 [1.32, 2.31]	1.62 [1.23, 2.14]	1.35 [1.00, 1.81]
3–0 months preconception	43	1.55 [1.15, 2.09]	1.45 [1.07, 1.95]	1.40 [1.03, 1.91]
Prenatal	81	1.10 [0.89, 1.37]	1.05 [0.84, 1.30]	1.11 [0.88, 1.39]
Trimester 1	27	1.29 [0.87, 1.89]	1.23 [0.84, 1.80]	1.12 [0.75, 1.66]
Trimester 2	23	1.02 [0.67, 1.53]	0.97 [0.64, 1.45]	0.95 [0.61, 1.46]
Trimester 3	31	1.02 [0.72, 1.45]	0.96 [0.68, 1.37]	1.25 [0.87, 1.79]

Note: Values in brackets are 95% confidence intervals. [a]The reference group consisted of offspring not exposed to stress in the exposure period studied. [b]Odds ratios in this column are adjusted for offspring's sex and birth order and 'mother's and father's age, highest level of education, country of origin, and criminal history. [c]Odds ratios in this column are additionally adjusted for ordinally represented gestational age at birth and small-for-gestational-age status.

Table 3. Results of Sensitivity Analyses Examining Preconception Stress Exposure

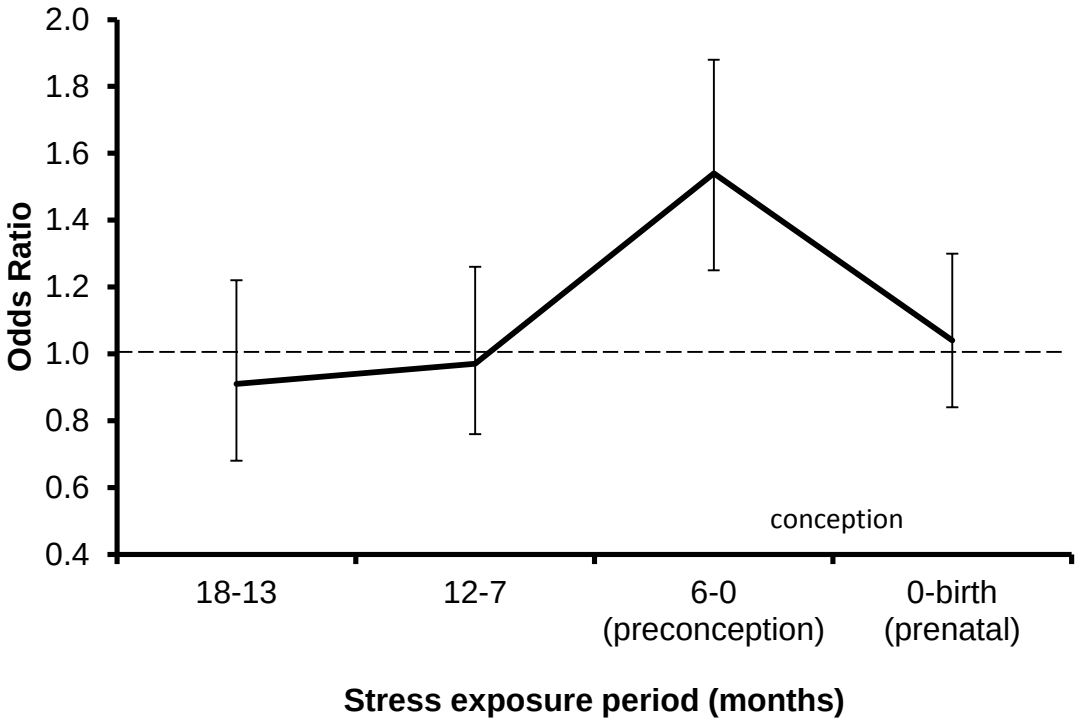
Model and analysis description	Offspring with stress exposure who died as infants (*n*)	Adjusted odds ratio
1. Analyses examining moderation by offspring sex		
Males exposed to preconception stress	62	1.83 [1.42, 2.35]
Females exposed to preconception stress	31	1.15 [0.81, 1.64]
2. Analyses examining specific timing of stress exposure		
18–13 months preconception	53	0.91 [0.68, 1.22]
12–7 months preconception	75	0.97 [0.76, 1.26]
3. Analysis including only low-risk offspring	45	1.61 [1.20, 2.17]
4. Analysis including only offspring of mothers with average (12–35 month) interpregnancy interval	25	2.09 [1.37, 3.21]
5. Analysis including only offspring with stress exposure due to death of maternal parent or sibling	64	1.31 [1.01, 1.69]
6. Analysis controlling for maternal smoking during pregnancy	52	1.35 [1.01, 1.81]

Note: Values in brackets are 95% confidence intervals. Odds ratios are adjusted for offspring's sex and birth order and mother's and father's age, country of origin, and criminal history. Low-risk offspring characteristics included full-term birth, normal birth weight, and normal weight for gestational age.

Figure Legend.

Figure 1. Risk (adjusted odds ratio) of infant mortality following maternal stress exposure during the preconception (18–13 months, 12–7 months, and 6–0 months before birth) and prenatal periods. Error bars represent 95% confidence intervals. The dashed reference line represents an odds ratio of 1.0, or no increased odds.

Figure 1.


2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
Odds Ratio
conception
18-13
12-7
6-0
(preconception)
0-birth
(prenatal)
Stress exposure period (months)

2.2 Offspring psychopathology following preconception, prenatal, and postnatal maternal bereavement stress

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Abstract

Background: Preconception, prenatal, and postnatal maternal stress are associated with increased offspring psychopathology, but findings are inconsistent and need replication. We estimated associations between maternal bereavement stress and offspring autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, schizophrenia, suicide attempt, and completed suicide.

Methods: Using Swedish registers, we conducted the largest population-based study to date examining associations between stress exposure in 738,144 offspring born 1992-2000 for childhood outcomes and 2,155,221 offspring born 1973-1997 for adult outcomes with follow-up through 2009. Maternal stress was defined as death of a first degree relative during 6 months before conception, across pregnancy, or the first two postnatal years. Cox proportional survival analyses were used to obtain hazard ratios (HR) in unadjusted and adjusted analyses.

Results: Marginal increased risk of bipolar disorder and schizophrenia following preconception bereavement stress was not significant. Third trimester prenatal stress increased risk of ASD (adjusted HR=1.58, 95% CI: 1.15-2.17) and ADHD (adjusted HR=1.31, 95% CI: 1.04-1.66). First postnatal year stress increased risk for offspring suicide attempt (adjusted HR=1.13, 95% CI: 1.02-1.25) and completed suicide (adjusted HR=1.51, 95% CI: 1.08-2.11). Bereavement stress during the second postnatal year increased risk of ASD (adjusted HR=1.30, 95% CI: 1.09-1.55).

Conclusions: Further research is needed on associations between preconception stress and psychopathological outcomes. Prenatal bereavement stress increases risk of offspring ASD and ADHD. Postnatal bereavement stress moderately increases risk of offspring suicide attempt,

completed suicide, and ASD. Smaller previous studies may have overestimated associations between early stress and psychopathological outcomes.

Keywords: stress; preconception; prenatal; postnatal; psychiatric; psychopathology; autism; attention-deficit/hyperactivity disorder; schizophrenia; suicide

In support of the developmental origins of disease hypothesis [1], accumulating evidence links maternal stress to increased risk of psychopathological morbidity in offspring [2-8]. Studies have identified associations with severe, impairing, and costly psychiatric disorders, including autism spectrum disorder [ASD; 9, 10], attention-deficit/hyperactivity disorder [ADHD; 8, 11, 12], and schizophrenia [2, 13]. Associations with adverse psychopathological outcomes have been reported following maternal exposure to physical stressors, such as famine [14, 15], and psychological stressors, such as bereavement [2-4], trauma [16], war [5], and natural disaster [17-19]. Assessing the effect of timing of an individual level, objective psychological stress on psychiatric outcomes is particularly important because linkage with a specifically-timed effect increases the likelihood that an association might be causal [20].

Previous research suggests that exposure during sensitive critical periods may exist for certain psychiatric disorders. For example, in humans *preconception* stress may be associated with an increased risk of childhood ADHD [21] and adult affective disorder [4], but only in male offspring. In rodents, preconception stress is associated with altered adult offspring memory functioning [22] and differences in affective and social behaviour [23]. In humans, evidence indicates that *prenatal* maternal stress is associated with psychopathological outcomes across stressors and populations [2-8, 10, 19, 24-27]. Additionally, *postnatal* stress exposure is associated with increased risk of offspring psychiatric outcomes [28-35].

While associations between early stress exposure and perinatal outcomes show relative consistency [27], associations between early maternal stress exposure and major psychopathological outcomes remain inconsistent and need focused and continued exploration for several reasons. First, there is a paucity of evidence for the effect of preconception maternal exposure to severe stress; where these do exist, effect sizes are modest at best [2, 4]. Second,

replication is needed for a number of reported effects. For example, a meta-analysis did not support an association between prenatal stress and schizophrenia [36], and studies predicting autism from prenatal stress also have been inconsistent [6, 10, 35, 37]. Finally, several important methodological issues limit the quality of much of the evidence to date. For example, measurement difficulties abound, such as the use of retrospective self-reports in small and biased samples [10]. In famine studies, individuals are exposed to psychological as well as nutritional stressors, while women that conceive and complete pregnancy during famine may represent an unusual group [8, 14, 38, 39]. These limitations are of enough concern to render current evidence for robust and/or causal associations between preconception, prenatal, and postnatal maternal stress exposure and offspring psychopathological outcomes inconclusive.

We set out to address sample size, measurement, and timing limitations in previous studies by analysing data from Swedish national registers. These data provide one of the largest and most comprehensive population registers currently available for psychiatric research. Utilising the highest quality and largest data set possible was necessary to draw conclusions regarding associations between rare risks and outcomes across several early risk periods in one population. We decided to focus on psychopathological outcomes with the best evidence to date (ASD, ADHD, and schizophrenia), associated outcomes of suicidal behaviour (suicide attempt and completed suicide), and bipolar disorder, which has not been directly examined previously. We defined exposure to maternal stress as the occurrence of the death of a first degree relative of the mother which we considered an objective measure of psychological stress. We also utilised the random nature of the timing of the exposure to bereavement stress in a quasi-experimental design [40], while statistically controlling for measured covariates to help account for alternative explanations.

We hypothesised that the findings would support prior positive findings by timing of exposure, as well as reveal novel associations with previously unstudied outcomes. In particular, we hypothesized that preconception bereavement stress would be associated with increased risk for offspring ADHD but not other outcomes [2, 3, 37]. We hypothesized that prenatal bereavement stress would be associated with increased risk for ADHD and schizophrenia [2, 3, 6, 14, 19, 41], as well as increased risk for bipolar disorder and attempted and completed suicide, but not ASD [35, 37]. Finally, we hypothesized that postnatal bereavement stress would be associated with increased risk for offspring ASD, ADHD [30, 33-35] and attempted and completed suicide [42]. We also performed sensitivity analyses to rule out moderation by offspring sex, test the robustness of associations by birth outcomes and parental psychopathology, and explore outcome specificity [43-51].

Methods

Study population

After approval from the Institutional Review Board and ethical committees at Karolinska Institutet and Indiana University, we constructed a population-based sample by linking Swedish nationwide, longitudinal population registries via unique personal identification numbers. The Medical Birth Registry [52, 53] included data on over 99% of all births in Sweden from 1973 to 2008 and was used to obtain information on gestational length and birth complications. First degree biological relatives of the mother (parents, full siblings, already born children) were identified using the Multi-Generation Registry [54]. The Cause of Death Registry was used to identify family member dates of death for bereavement stress exposure indication. The National Patient Register provided diagnosis for all inpatient hospital admissions since 1973 and

outpatient since 2001. The Education Register [55] provided information on parental highest level of completed formal education, and the National Crime Register [56] provided data on parental criminal convictions since the age of 15, the Swedish age of criminal responsibility, from 1973 onward. Finally, the Migration Register provided information on dates of migration in or out of Sweden.

Figure 1 presents the sample flow across child and adult specific samples. The dataset began with 2,842,683 individuals born from 1973 to 2000. We removed multiple births because rates of adverse birth outcomes in multiples differs from singletons [57], and offspring with missing mother, grandmother, and father identification numbers for complete identification of family members that may have died during the exposure window. We also removed offspring with missing gestational age and possible erroneous gestational age values of greater than 42 weeks and 6 days because timing of stress exposure was determined by gestational age at birth. A total of 2,411,725 (84.8%) singleton offspring remained before separating by year of birth for child and adult outcome samples.

Valid and reliable childhood outcomes from the National Patient Register were available for offspring born from 1992 to 2000 (n=742,947). Children had to be at least 2 years old to receive a diagnosis of ASD or ADHD. We removed children that had died, emigrated, or were diagnosed before their second birthday and or were missing a diagnosis date. Thus, our final child sample contained 738,144 offspring. No offspring were diagnosed with ASD or ADHD before exposure to stress in the second postnatal year. Adult outcomes were limited to a cohort of offspring born between 1973 and 1997 (n=2,197,707) to allow offspring to reach 12 years of age to receive a valid diagnosis age. Similar to the child outcome sample, we removed adults who died, emigrated, presented with an adult-onset outcome before their twelfth birthday, or

were missing their date of diagnosis resulting in a final sample of 2,155,221 adults. Both cohorts were followed through 2009.

Exposure

Death of a first degree relative was chosen to provide an insult that resulted in substantial psychological stress [58] with precise timing. For preconception bereavement stress, this included death of her biological parents, siblings, or already born children; for prenatal and postnatal bereavement stress, this definition was extended to include death of the biological father of the index child.

Exposure periods were divided into preconception (6-0 months prior to conception) and was further subdivided into 0-3 months and 4-6 months preconception windows; prenatal (conception to birth) and further subdivided into trimesters (1st trimester 0-12 weeks; 2nd trimester 13-24 weeks; and 3rd trimester 25 weeks to birth); and postnatal (0-2 years) which was subdivided into first year and second year windows. See Table 1 for details concerning the number of exposed individuals across the risk periods. For the few mothers (32 preconception, 25 prenatal, 34 first postnatal year, and 66 second postnatal year) that experienced more than one stressor within the same exposure window, the timing of the first stress exposure was used. Less than 0.01% of the sample experienced a stressor during more than one exposure windows. Sample size restricted further investigation of possible stress exposure dosage effects.

Outcome variables

The National Patient Register provided discharge date and primary diagnosis using WHO's International Classification of Diseases (ICD-8, -9, and -10).

Childhood psychiatric outcomes

Children receiving an ASD diagnosis included inpatient and outpatient diagnoses of ASD and Asperger's syndrome (ICD-10: F84). Children receiving an ADHD diagnosis included inpatient or outpatient diagnosis of hyperkinetic disorder (ICD-10: F90).

Adult psychiatric outcomes

We identified bipolar disorder (ICD-8: 296 excluding 296.20, 296.4-296.7; ICD-9: 296A, C, D, E, W; ICD-10: F30, 31) and strictly defined schizophrenia [ICD-8: 295 excluding 295.40, 295.50. 295.70; ICD-9: 295 excluding 295E, 295F, 295H; ICD-10: F20; 59]. We also identified suicide attempt that resulted in inpatient hospitalisation and completed suicide [ICD-8: E950-959, E980-989; ICD-9: E950-959, E980-989; ICD-10: X60-84, Y10-34, Y870, Y872; 60]. For individuals presenting with multiple suicide attempts, only the first occasion was counted. We chose not to examine broadly defined affective disorder because hospitalisation for that diagnosis may indicate suicidality or psychosis and be better examined when categorised as such.

Analyses

We used Cox proportional survival analyses to estimate the association of early bereavement stress on right-censored psychiatric outcomes using SAS 9.2. Information on migration and death were used to calculate person-years at risk for receiving a diagnosis; if offspring did not receive a diagnosis within the study period, they contributed person-time at risk until death, emigration, or the end date of follow-up (December 31, 2009), whichever came first. For each outcome, unadjusted and adjusted estimates were fitted using dichotomous predictors for each preconception, prenatal, and postnatal stress exposure. Robust standard errors were utilized in baseline and adjusted models to account for the nested nature of the data (the possibility of one mother having multiple children within the dataset).

Adjusted models controlled for the following potential confounders: offspring sex, birth order (first [referent], second, third, fourth born and higher), offspring birth weight, (missing, 500-2499, and ≥ 2500-6000 [referent] g), gestational age (23-32.6, 33-36.6, 37-41.6 [referent], and 42+ weeks), maternal and paternal age (< 20, 20-24, 25-29 [referent], 30-34, and > 34 years), maternal and paternal country of birth (Swedish [referent], non-Swedish, or missing), maternal and paternal highest education (primary or lower secondary education of 9 or fewer years, 1-3 years of upper secondary school [referent], post-secondary education, and missing), a binary indicator of maternal and paternal history of any criminal conviction, a binary indicator of both maternal and paternal history of severe mental illness (including bipolar disorder, broadly defined schizophrenia, and suicide attempt resulting in inpatient care), and a binary indicator of both maternal and paternal death by suicide.

Sensitivity analyses

First, we tested whether offspring sex moderated the association between bereavement stress and outcome by including an offspring sex by exposure interaction term because previous research has indicated that sex differences may exist in some of these associations [3, 4]. Second, we included only offspring whose parents did not have a history of severe psychopathology, including bipolar disorder, broadly defined schizophrenia, suicide attempt, or completed suicide, to control more rigorously for familial risk of psychopathology. Third, we restricted the analysis to full term (≥37 and < 43 weeks gestation) and normal birth weight (≥ 2500g) because these obstetric factors are associated with both maternal exposure to stressors and excess risk of later psychopathology [43, 51, 61-64]. Fourth, we predicted broadly defined schizophrenia, including schizoaffective disorder and non-affective psychosis (ICD-8: 295, 297, 298.20-298.99, 299.99; ICD-9: 295, 297, 298C-X; ICD-10: F20-29), in order more precisely replicate or refute previous

research [2]. Finally, we combined bipolar disorder and strictly defined schizophrenia into severe mental illness because of the shared genetic aetiology of these disorders [59]. This test explored if associations were outcome-specific or if early stress constitutes a shared risk factor.

Results

We identified a total of 6,430 children with ASD [Kaplan-Meier estimate (K-M est) = 1.2% by the age 17.9 years; 72.4% male] and 14,313 children with ADHD (K-M est = 2.7% by age 17.9 years; 75.8% male) within the child sample. We identified 8,001 individuals with bipolar disorder (K-M est = 0.9% by age 35 years; 68.5% male), 8,063 with non-affective psychoses (K-M est = 0.8% by age 35 years; 57.9% male), 2,400 individuals with schizophrenia (K-M est = 0.3% by age 35 years; 66.5% male), 25,855 cases of attempted suicide that resulted in inpatient hospital care (K-M est = 1.9% by age 35 years; 34.0% male), and 1,751 cases of completed suicide (K-M est = 0.2% by age 35 years) in the adult sample.

Preconception maternal stress

Table 2 presents the results from the survival analyses. We found no significant associations between preconception bereavement stress and offspring child or adult disorders. The magnitude of association with bipolar disorder and schizophrenia remained marginally elevated in adjusted models, but not statistically significantly elevated. In spite of the size of our sample, lack of a statistically significant estimate in a low number of exposed cases ($n_{bipolar}$=73, $n_{schizophrenia}$=24) may suggest that the association is too weak to be found in small numbers. Separating the preconception period into two 3-month windows (0-3 mo and 4-6 mo preconception) echoed the null associations seen across the entire six month window.

Prenatal maternal stress

Table 3 shows associations with exposure to prenatal maternal stress. A statistically significant association was found for offspring ASD (adjusted HR = 1.30, 95% CI: 1.04-1.62). No other significant associations were found for the analysis across the entire prenatal period.

Analyses by trimester (Table 3) suggested that the association between prenatal maternal exposure to stress and increased risk for offspring ASD may be driven by risk incurred from third trimester exposure (adjusted HR = 1.58, 95% CI: 1.15-2.17). An elevated risk, however, was also noted following first trimester stress exposure, although the confidence interval around the association was large (adjusted HR = 1.25, 95% CI: 0.82-1.91). Risk for ADHD was significantly increased following third trimester stress exposure (adjusted HR = 1.31, 95% CI: 1.04-1.66). No other significant associations by trimester were found.

Postnatal maternal stress

Table 4 presents associations with postnatal maternal stress. Over the first two postnatal years, maternal exposure to bereavement stress marginally increased risk of offspring ASD (adjusted HR = 1.15, 95% CI: 1.00-1.32) and suicide attempt (adjusted HR = 1.10, 95% CI: 1.03-1.18). When separated by postnatal year of exposure, offspring of women who experienced stress in the first postnatal year were at increased risk of suicide attempt (adjusted HR = 1.13, 95% CI: 1.02-1.25) and completed suicide (adjusted HR = 1.51, 95% CI: 1.08-2.11). Maternal stress during the second postpartum year was associated with a significant increased risk of ASD (adjusted HR = 1.30, 95% CI: 1.09-1.55). No other significant associations between postnatal maternal stress and offspring psychiatric outcomes were found.

Sensitivity analyses

First, no sex interaction was statistically significant (all results available upon request). Results from the second and third sensitivity analyses, restricting the sample to offspring whose

parents had no history of severe mental illness or completed suicide and restricting the sample to offspring to full term and normal birth weight respectively, paralleled findings from original models. Fourth, no notable or significant associations with broadly defined schizophrenia were found across any exposure period. Finally, results predicting combined severe mental illness revealed that preconception estimates remained elevated and the association trended towards statistical significance (adjusted HR = 1.18, 95% CI: 0.96-1.45, N=92).

Discussion

Using one of the largest population databases currently available, we examined the effect of preconception, prenatal, and early postnatal maternal bereavement stress on risk of child and adult psychopathology. Our data point to three key findings: First, in contrast with some previous studies [2, 4, 7, 27], we found few associations between a well-characterised, objective measure of early maternal exposure to psychological stress and odds of later severe psychiatric problems. Second, associations reported are dependent on the timing of the exposure and on the particular outcome assessed. Third, in line with previous findings [6, 10, 19, 65], excess risk following maternal prenatal bereavement stress was identified for childhood onset developmental disorders, namely ASD and ADHD. We also identified novel associations between postnatal maternal bereavement exposure and offspring attempted and completed suicide and ASD. Generally, these findings suggest that previous research may have overestimated the magnitude of associations identified.

We report no statistically significant effect of preconception stress on any of the studied outcomes. However, the effect sizes and parallel findings from sensitivity analyses suggest that marginal associations may be present for severe mental illness [i.e. bipolar disorder and

schizophrenia combined; 59]. Increased numbers of exposed cases would allow for better precision in estimating effects. Our preconception null results are consistent with previous findings for ASD [37], but inconsistent with a previous study predicting ADHD [3]. These authors defined ADHD by diagnosis and/or medication, found significant association only in male offspring, and only following the unexpected death of a spouse or already born child.

We found evidence for an association between prenatal bereavement stress and offspring ASD and ADHD only. Estimates were highest following third trimester exposure. The associations with ASD remained significant after adjustment for potential confounders and in all of the sensitivity analyses. Similar positive associations with ASD have been reported in studies measuring potentially less severe but more chronic stress exposure from family discord [65], after hurricanes and tropical storm exposure [19], and retrospectively recalled [10] and prospectively measured [6] stressful life events. In contrast, others have not identified increased odds of ASD following stress exposure in a large Danish cohort [37] and in a somewhat smaller study using a broader definition of stress [35]. Unlike previous studies (Li et al., 2010, Rodriguez and Bohlin, 2005), we did not identify moderation by offspring sex. More research is needed to clarify this.

Our findings are not consistent with previous studies reporting associations between maternal anxiety, prenatal stress exposure or potentially non-independent life events, and subsequent neurodevelopmental or behavioural problems in infants and children [27]. Many of these associations may be confounded by genetic transmission of temperament from mother to child (King *et al.* 2005), although some have taken these effects into account (Charil et al., 2010). It may be that specific symptoms, such as cognitive and language deficits, are more likely to have a positive association with prenatal stress exposures than the disorders we examined

[e.g., 18, 24, 66, 67]. However, this would imply more discontinuity between child neurodevelopment or behaviour and mental health outcomes than might be expected [68, 69].

ASD and ADHD are comorbid conditions [70], and prenatal stress may act as a shared risk factor for abnormal neurodevelopment [71]. This notion, however, is inconsistent with our lack of association with adult neurodevelopmental outcomes. In our larger sample, we do not replicate the first trimester association with broadly defined schizophrenia [2]. Our findings on bipolar disorder are consistent with a null finding between prenatal stress and affective disorder, including bipolar disorder [5]. To our knowledge, this is the first study to have examined the association between prenatal bereavement stress and offspring suicidal behaviour. Overall, our findings do not support even moderate effects of prenatal bereavement stress on risk of adult psychiatric outcomes.

Postnatal maternal bereavement stress increased the risk for offspring suicide attempt and completed suicide, in line with previous research on childhood trauma and later suicidal behaviour [28, 29]. Maternal exposure to bereavement stress in the second postnatal year was also associated with increased odds of ASD and the association was robust in offspring without parental history of severe mental illness or adverse birth outcome [35]. Unlike the shared ASD/ADHD patterns identified following prenatal stress, associations between postnatal stress and ADHD were not consistently statistically significant. Thus, different mechanisms may be responsible for the postnatal and prenatal associations with ASD.

Determining if outcomes are associated with particular sensitive periods of development may offer insight into aetiological mechanisms [28, 71-77]. If prenatal associations with ASD are replicated, future research should examine mechanisms specific to late pregnancy relevant to the risk of psychopathology, including development of olivary neurons and Purkinje cells in the

cerebellum [78-80] or oestradiol-sensitive gene expression [41]. Postnatal developmental changes in the prefrontal cortex [81] or susceptibility to diminished parenting resources, sensitivity, and/or stimulation as a consequence of maternal stress [82, 83] may be particularly critical for ASD risk during the second postnatal year of development [84]. Future research may also consider differential susceptibility to stressors given that family members of individuals with ASD show elevated rates of anxiety [85], which may be related to stress reactivity. General mechanisms linking prenatal stress exposure and ADHD may include a disruption in stress-response systems [71, 75], prefrontal cortex development [86], gray matter density development [76], or confounding inherited factors that are associated both with the odds of stress exposure and offspring psychopathology [87]. Postnatally, exposure to trauma, stress and maternal depression [82, 88] may adversely affect offspring problem-solving abilities, cognitive ability, attachment, and/or compound genetic vulnerability to suicide [42, 83, 89, 90].

This study has several methodological strengths. We describe the associations between preconception, prenatal, and postnatal maternal stress exposures and offspring risk for later psychiatric morbidity in the largest population cohort to date. We use a precise measurement of severe psychological stress, include validated measures of psychopathological outcomes, and control for important child, family, and parental confounds. Notwithstanding, several limitations need to be considered and addressed in future research. For example, death of a relative causes a subjective level of stress that varies by individual and circumstance. Therefore, such stress may endure over a variable length of time and we are making assumptions about the relevant period of stress. It is possible that death of a relative provides psychological relief in cases of death due to a long-term illness [91]. Mothers who are bereaved might also experience other unmeasured stressors (e.g. economic or social) or modify relevant aspects of their behaviour (e.g. increase

alcohol intake) in response to the bereavement, which may influence the associations [92]. Studies that can reliably measure a mother's subjective experience of stress may be invaluable for understanding potential mechanisms through which early life experiences influence later outcomes. Although we utilised the largest sample to date, relatively low numbers of exposed cases resulted in some wide confidence intervals. Given that we performed a high number of analyses, the likelihood of identifying a significant association by chance is high. Future research predicting symptom counts and neuropsychiatric or neurocognitive outcomes rather than diagnostic categories may help to compare the findings to previous research, improve statistical power, and enhance generalizability. Finally, while we identified statistically significant associations, such epidemiological associations cannot be said to be causal, given the complexity of unmeasured factors. Other quasi-experimental designs, such as sibling comparisons, could be used in future research to strengthen causal inferences [20, 93].

Overall, we report little influence of preconception, prenatal, and postnatal maternal stress exposure on risk of major psychiatric outcomes. This contrasts with reports from previous, less robust evidence. Only a moderately increased risk was found for childhood developmental disorders, namely ASD and ADHD, following prenatal third trimester exposure, and, for ASD, suicide attempt, and completed suicide following early postnatal exposure. Future research should attempt to replicate these findings, explore the underlying mechanisms, and examine the specificity of the type, timing, and severity of maternal stressors.

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Table 1. Descriptive characteristics of all Swedish, live-born, singleton offspring across child (A) and adult (B) outcome samples by maternal stress exposure status.

	A. Child Outcomes Sample: born 1992-2000 (n=738,144)				B. Adult Outcomes Sample: born 1973-1997 (n=2,155,221)			
	Stress Exposure Period				Stress Exposure Period			
Characteristic (n, %)	None	Preconception	Prenatal	Postnatal	None	Preconception	Prenatal	Postnatal
N	707361	4944	6625	19592	2060313	15799	19903	60223
Female Offspring	344779 (48.7)	2417 (48.9)	3249 (49.0)	9488 (48.4)	1002197 (48.6)	7706 (48.8)	9710 (48.8)	29457 (48.9)
Birth Order								
First*	295710 (41.8)	1320 (26.7)	2232 (33.7)	6669 (34.0)	871133 (42.3)	4163 (26.4)	6600 (33.2)	20722 (34.4)
Second	264985 (37.5)	1899 (38.4)	2387 (36.03)	7162 (36.6)	764177 (37.1)	6108 (38.7)	7438 (37.4)	22417 (37.2)
Third	104759 (14.8)	1124 (22.7)	1301 (19.6)	3669 (18.7)	311043 (15.1)	3766 (23.8)	4020 (20.2)	11519 (19.1)
Fourth or more	41907 (5.9)	601 (12.2)	705 (10.7)	2092 (10.7)	113959 (5.5)	1762 (11.0)	1845 (9.3)	5565 (9.2)
Gestational length (weeks)								
22-27.6	926 (0.1)	10 (0.2)	10 (0.2)	34 (0.2)	2005 (0.1)	17 (0.1)	16 (0.1)	75 (0.1)
28-30.6	1891 (0.3)	23 (0.5)	19 (0.3)	81 (0.4)	5014 (0.2)	57 (0.4)	43 (0.2)	198 (0.3)
31-33.6	5105 (0.7)	47 (1.0)	38 (0.6)	161 (0.8)	14522 (0.7)	136 (0.9)	137 (0.7)	522 (0.9)
34-36.6	25959 (3.7)	235 (4.8)	232 (3.5)	768 (3.9)	76801 (3.7)	691 (4.4)	762 (3.8)	2483 (4.1)
37-42.6*	673480 (95.2)	4629 (93.6)	6326 (95.5)	18548 (94.7)	1961971 (95.2)	14898 (94.3)	18945 (95.2)	56945 (94.6)
Birth weight (g)								
missing	2086 (0.3)	12 (0.2)	16 (0.2)	60 (0.3)	4981 (0.2)	27 (0.2)	49 (0.3)	158 (0.3)
500 - 2499	21174 (3.0)	195 (3.9)	207 (3.1)	686 (3.5)	67819 (3.3)	638 (4.0)	702 (3.5)	2327 (3.9)
2500 - 4499*	684101 (96.7)	4737 (95.8)	6402 (96.6)	18846 (96.2)	1987513 (96.5)	15134 (95.8)	19152 (96.2)	57738 (95.9)
Maternal Age (years)								
< 20	14448 (2.0)	50 (1.0)	83 (1.3)	260 (1.3)	79241 (3.9)	324 (2.1)	453 (2.3)	1363 (2.3)
20-24	123749 (17.5)	551 (11.1)	719 (10.9)	2007 (10.2)	515551 (25.0)	2751 (17.4)	3146 (15.8)	9600 (15.9)
25-29*	268893 (38.0)	1431 (28.9)	1859 (28.1)	5574 (28.5)	785665 (38.1)	5310 (33.6)	6527 (32.8)	19993 (33.2)
30-34	209476 (29.6)	1669 (33.8)	2261 (34.1)	6762 (34.5)	488889 (23.7)	4674 (29.6)	5991 (30.1)	18224 (30.3)
≥ 35	90795 (12.8)	1243 (25.1)	1703 (25.7)	4989 (25.5)	190967 (9.3)	2740 (17.3)	3786 (19.0)	11043 (18.3)
Paternal Age (years)								
missing	584 (0.1)	2 (0.0)	6 (0.1)	29 (0.2)	1884 (0.1)	17 (0.1)	17 (0.1)	80 (0.1)
< 20	4188 (0.6)	17 (0.3)	24 (0.4)	82 (0.4)	17281 (0.8)	73 (0.5)	97 (0.5)	312 (0.5)
20-24	64025 (9.1)	295 (6.0)	405 (6.1)	1126 (5.8)	278453 (13.5)	1442 (9.1)	1680 (8.4)	5295 (8.8)
25-29*	221051 (31.3)	1164 (23.5)	1471 (22.2)	4448 (22.7)	714983 (34.7)	4489 (28.4)	5394 (27.1)	16424 (27.3)
30-34	235552 (33.3)	1648 (33.3)	2081 (31.4)	6488 (33.1)	624736 (30.3)	5079 (32.2)	6350 (31.9)	19391 (32.2)
≥ 35	182545 (25.8)	1820 (36.8)	2644 (39.9)	7448 (38.0)	422976 (20.5)	4699 (29.9)	6365 (32.0)	18721 (31.1)
Maternal highest education								
missing	281 (0.0)	4 (0.1)	7 (0.1)	12 (0.1)	1756 (0.1)	10 (0.1)	14 (0.1)	200 (0.3)
≤ 9 years	54342 (7.7)	475 (9.6)	664 (10.0)	2053 (10.5)	272846 (13.2)	2490 (15.8)	3185 (16.0)	9602 (15.9)
1-3 years upper secondary*	178733 (25.3)	2576 (52.1)	3410 (51.5)	10054 (51.3)	1060344 (51.5)	7874 (49.8)	9900 (49.7)	29978 (49.8)
Post secondary	285652 (40.4)	1889 (38.2)	2544 (38.4)	7473 (38.1)	725367 (35.2)	5425 (34.3)	6804 (34.2)	20443 (34.0)
Paternal highest education								
missing	1614 (0.2)	11 (0.2)	20 (0.3)	69 (0.4)	9032 (0.4)	68 (0.4)	235 (1.2)	671 (1.1)
≤ 9 years	95271 (13.5)	741 (15.0)	1043 (15.7)	3204 (16.4)	453530 (22.0)	3699 (23.4)	4751 (23.9)	14580 (24.2)
1-3 years upper secondary*	387182 (54.7)	2725 (55.1)	3512 (53.0)	10283 (52.5)	1020115 (49.5)	7579 (48.0)	9406 (47.3)	28288 (47.0)
Post secondary	223294 (31.6)	1467 (29.7)	2050 (30.9)	6036 (30.8)	577636 (28.0)	4453 (28.2)	5511 (27.7)	16684 (27.7)
Maternal Swedish Nationality	675121 (95.4)	4773 (96.5)	6372 (96.2)	18841 (96.2)	1985462 (96.4)	15342 (97.1)	19325 (97.1)	58549 (97.2)
Paternal Swedish Nationality	643012 (91.0)	4479 (90.6)	6023 (91.0)	17740 (90.7)	1909901 (92.8)	14619 (92.6)	18394 (12.6)	55630 (92.5)
missing	584 (0.1)	2 (0.0)	6 (0.1)	29 (0.2)	1884 (0.0)	17 (0.1)	17 (0.1)	80 (0.1)
Maternal criminal history	82974 (11.7)	693 (14.0)	964 (14.6)	2764 (14.1)	229640 (11.2)	1904 (12.1)	2501 (12.3)	7465 (12.4)
Paternal criminal history	293483 (41.5)	2145 (43.4)	2895 (43.7)	8515 (43.5)	797719 (38.7)	6029 (38.2)	7714 (38.8)	23449 (38.9)
Maternal psychopathology	23874 (3.4)	182 (3.7)	307 (4.6)	840 (4.3)	76420 (3.7)	619 (3.9)	889 (4.5)	2569 (4.3)
Paternal psychopathology	17044 (2.4)	142 (2.9)	218 (3.3)	627 (3.2)	60781 (3.0)	486 (3.1)	644 (3.2)	2114 (3.5)
Maternal completed suicide	399 (0.1)	4 (0.1)	11 (0.2)	52 (0.3)	3231 (0.2)	30 (0.2)	30 (0.2)	173 (0.3)
Paternal completed suicide	1326 (0.2)	16 (0.3)	60 (0.9)	226 (1.2)	9737 (0.5)	74 (0.5)	172 (0.9)	622 (1.0)

Note: *Reference. Pregestational stress period is from 6-0 mo before conception, prenatal period is from conception to birth, postnatal period is from birth to second birthday.

Table 2. Risk for child and adult neuropsychiatric outcomes associated with preconception maternal stress exposure within the six months prior to conception.

	Across 6-0 mo preconception					6-4 mo preconception					3-0 mo preconception				
	N	Unadjusted		Adjusted*		N	Unadjusted		Adjusted*		N	Unadjusted		Adjusted*	
Outcome	exposed	HR	95% CI	HR	95% CI	exposed	HR	95% CI	HR	95% CI	exposed	HR	95% CI	HR	95% CI
ASD	40	0.91	0.67-1.24	0.88	0.64-1.19	17	0.76	0.47-1.22	0.72	0.45-1.16	23	1.07	0.71-1.61	1.04	0.69-1.56
ADHD	91	0.93	0.76-1.14	0.9	0.73-1.10	45	0.90	0.67-1.21	0.86	0.64-1.16	46	0.96	0.72-1.28	0.93	0.70-1.24
Bipolar	73	1.24	0.98-1.56	1.20	0.95-1.51	36	1.18	0.85-1.64	1.14	0.82-1.58	37	1.30	0.94-1.80	1.26	0.91-1.74
Schizophrenia	24	1.36	0.91-2.03	1.32	0.88-1.97	13	1.42	0.83-2.45	1.39	0.81-2.40	11	1.29	0.71-2.33	1.24	0.69-2.25
Suicide Attempt	175	0.92	0.79-1.06	0.88	0.76-1.02	98	1.00	0.82-1.21	0.95	0.78-1.16	77	0.83	0.66-1.03	0.80	0.64-1.01
Completed Suicide	8	0.62	0.31-1.23	0.61	0.30-1.21	5	0.74	0.31-1.79	0.73	0.30-1.76	3	0.48	0.15-1.48	0.47	0.15-1.46

*Adjusted for offspring sex, birth order, birth weight, gestational age, maternal and paternal age, highest education, nationaliy, criminality, severe psychopathology, and completed suicide.

Table 3. Risk for child and adult neuropsychiatric outcomes associated with prenatal maternal stress exposure across pregnancy and by trimester.

	Across Pregnancy					Trimester 1					Trimester 2					Trimester 3				
	N	Unadjusted		Adjusted*		N	Unadjusted		Adjusted*		N	Unadjusted		Adjusted*		N	Unadjusted		Adjusted*	
Outcome	exposed	HR	95% CI	HR	95% CI	exposed	HR	95% CI	HR	95% CI	exposed	HR	95% CI	HR	95% CI	exposed	HR	95% CI	HR	95% CI
ASD	79	**1.36**	**1.09-1.70**	**1.30**	**1.04-1.62**	22	1.32	0.87-2.00	1.25	0.82-1.91	18	1.00	0.63-1.59	0.97	0.61-1.53	39	**1.67**	**1.22-2.28**	**1.58**	**1.15-2.17**
ADHD	149	1.15	0.98-1.35	1.12	0.95-1.32	34	0.91	0.65-1.28	0.87	0.62-1.23	45	1.12	0.84-1.50	1.10	0.82-1.47	70	**1.34**	**1.06-1.70**	**1.31**	**1.04-1.66**
Bipolar	73	1.00	0.79-1.25	0.96	0.76-1.21	16	0.79	0.48-1.29	0.76	0.46-1.24	27	1.20	0.82-1.74	1.14	0.78-1.66	30	0.98	0.69-1.41	0.95	0.67-1.37
Schizophrenia	18	0.82	0.51-1.30	0.78	0.49-1.24	1	0.17	0.02-1.17	0.16	0.02-1.10	8	1.18	0.59-2.36	1.13	0.56-2.26	9	0.98	0.51-1.89	0.94	0.49-1.80
Suicide Attempt	251	1.06	0.93-1.20	1.04	0.92-1.17	59	0.89	0.69-1.15	0.86	0.67-1.12	77	1.05	0.84-1.31	1.03	0.82-1.29	115	1.16	0.97-1.40	1.16	0.97-1.40
Completed Suicide	15	0.93	0.56-1.55	0.92	0.56-1.54	4	0.90	0.34-2.40	0.88	0.33-2.35	4	0.81	0.30-2.15	0.80	0.30-2.14	7	1.05	0.50-2.20	1.04	0.50-2.19

*Adjusted for offspring sex, birth order, birth weight, gestational age, maternal and paternal age, highest education, nationaliy, criminality, severe psychopathology, and completed suicide.

Table 4. Risk for child and adult neuropsychiatric outcomes associated with postnatal maternal stress exposure across the first two postnatal years and separated by year.

		Across first two years					**First year**					**Second year**				
	N	Unadjusted		Adjusted*		N	Unadjusted		Adjusted*		N	Unadjusted		Adjusted*	
Outcome	exposed	HR	95% CI	HR	95% CI	exposed	HR	95% CI	HR	95% CI	exposed	HR	95% CI	HR	95% CI
ASD	209	**1.21**	**1.06-1.39**	**1.15**	**1.00-1.32**	85	1.04	0.84-1.29	0.99	0.80-1.22	124	**1.37**	**1.15-1.64**	**1.30**	**1.09-1.55**
ADHD	426	**1.11**	**1.01-1.22**	1.06	0.96-1.17	189	1.03	0.90-1.19	1.00	0.86-1.15	237	**1.17**	**1.03-1.33**	1.11	0.98-1.27
Bipolar	214	0.97	0.85-1.11	0.93	0.81-1.07	109	1.03	0.86-1.25	1.00	0.83-1.21	105	0.91	0.75-1.11	0.87	0.72-1.06
Schizophrenia	76	1.15	0.92-1.45	1.09	0.87-1.37	35	1.11	0.80-1.55	1.06	0.76-1.48	41	1.19	0.88-1.62	1.12	0.82-1.53
Suicide Attempt	801	**1.12**	**1.04-1.20**	**1.10**	**1.03-1.18**	389	**1.14**	**1.03-1.26**	**1.13**	**1.02-1.25**	412	**1.10**	**1.00-1.21**	1.07	0.97-1.18
Completed Suicide	55	1.14	0.87-1.49	1.12	0.86-1.47	35	**1.52**	**1.09-2.12**	**1.51**	**1.08-2.11**	20	0.79	0.51-1.23	0.77	0.50-1.20

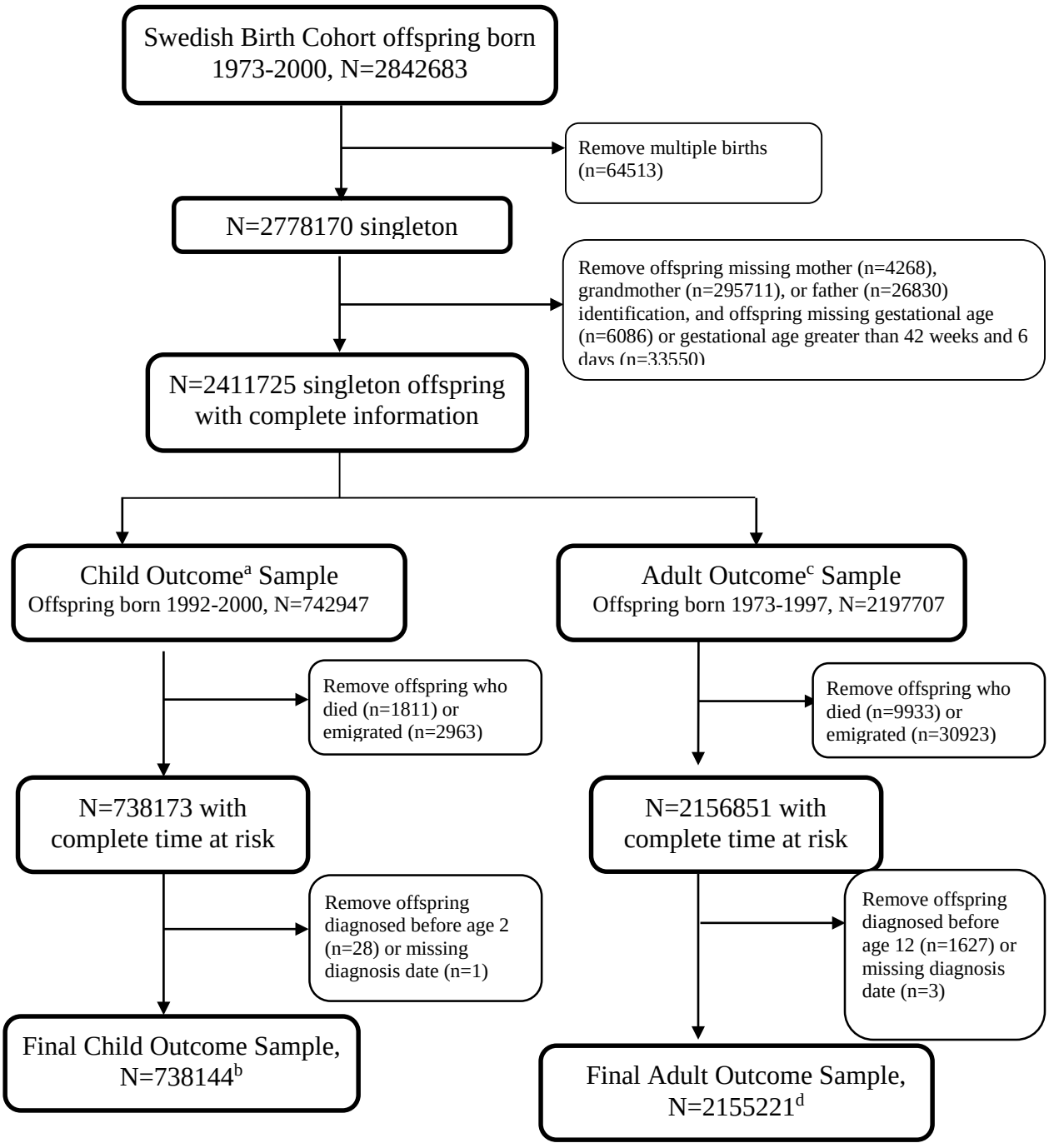
*Adjusted for offspring sex, birth order, birth weight, gestational age, maternal and paternal age, highest education, nationaliy, criminality, severe psychopathology, and completed suicide.

Figure Legend

Figure 1. Participant selection flow from the Swedish birth cohort through child and adult outcomes samples that were restricted by birth years and quality of neuropsychiatric outcomes.

Note: [a]Child outcomes include ADHD and ASD. [b]Table 1 (A) provides demographic information on child outcome sample. [c]Adult outcomes include bipolar disorder, schizophrenia, suicide attempt, and completed suicide. [d]Table 1 (B) provides demographic information on adult outcome sample.

Figure 1.


Swedish Birth Cohort offspring born 1973-2000, N=2842683
Remove multiple births (n=64513)
N=2778170 singleton
Remove offspring missing mother (n=4268), grandmother (n=295711), or father (n=26830) identification, and offspring missing gestational age (n=6086) or gestational age greater than 42 weeks and 6 days (n=33550)
N=2411725 singleton offspring with complete information
Child Outcome[a] Sample
Offspring born 1992-2000, N=742947
Adult Outcome[c] Sample
Offspring born 1973-1997, N=2197707
Remove offspring who died (n=1811) or emigrated (n=2963)
Remove offspring who died (n=9933) or emigrated (n=30923)
N=738173 with complete time at risk
N=2156851 with complete time at risk
Remove offspring diagnosed before age 2 (n=28) or missing diagnosis date (n=1)
Remove offspring diagnosed before age 12 (n=1627) or missing diagnosis date (n=3)
Final Child Outcome Sample, N=738144[b]
Final Adult Outcome Sample, N=2155221[d]

2.3 Birth weight, physical morbidity, and mortality: A population-based sibling-comparison study

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Abstract

Associations between low birth weight (≤ 2500) and increased risk of mortality and morbidity provided the foundation for the Developmental Origins of Health and Disease Hypothesis. Previous between-family studies could not control for unmeasured confounds. Therefore, we compared differentially exposed siblings to estimate the extent to which the associations were due to uncontrolled factors. Our population cohort included 3,291,773 individuals born in Sweden from 1973-2008. Analyses controlled for gestational age among other covariates and considered birth weight as ordinal and continuous. Outcomes included mortality after one year, cardiac-related death, hypertension, ischemic heart disease, pulmonary circulation problems, stroke, and type 2 diabetes mellitus. We fit fixed effects models to compare siblings and sensitivity analyses to test alternative explanations. Across the population, the lower the birth weight, the greater the risk for mortality [e.g., cardiac-related death (Hazard Ratio $_{\text{Low Birth Weight}}$ =2.69, 95% confidence interval: 2.05, 3.53)] and morbidity [e.g., type 2 diabetes mellitus (Hazard Ratio $_{\text{Low Birth Weight}}$ =1.79, 95% confidence interval: 1.50, 2.14)] outcomes. All associations were independent of shared familial confounds and measured covariates. Results emphasize the importance of birth weight as a risk factor for subsequent mortality and morbidity.

Keywords: birth weight, cardiovascular diseases, diabetes mellitus, fetal development, stroke

Based on the seminal work by Barker [1], the Developmental Origins of Health and Disease hypothesis postulates that low birth weight, a proxy of fetal growth, causally impacts several of the most costly and burdensome [2, 3] non-communicable diseases. Low birth weight is associated with offspring mortality [4] and physical morbidity, including increased risk for cardiovascular disease [5-10], hypertension [11-17], type 2 diabetes mellitus [18], and stroke [15, 19]. The associations are present across populations and research has identified plausible biological mechanisms that mediate the associations [1, 20-22].

The commonly held assumption that low birth weight causally impacts adverse adult outcomes, however, needs to be rigorously tested as alternative explanations exist. The field continues to struggle with inferring causation from correlation [23] and conflicting results across non-communicable disease outcomes have been reported [11, 24-28]. The previously identified associations may be due to unmeasured selection factors, such as environmental confounding and/or shared genetic liability, that influence both the likelihood of experiencing low birth weight and the outcomes [23, 29-31]. For example, low birth weight is associated with environmental risks that are themselves predictive of subsequent adverse outcomes [15]. Family, twin, and genome-wide linkage analyses also indicate that genetic factors influence birth weight and fetal growth [30, 32-36], as well as the studied outcomes [37]. As such, research needs to rule out plausible environmental and genetic confounds that may be responsible for the associations between low birth weight and mortality and morbidity. Determining accurate estimates of associations and testing alternative hypotheses is therefore essential [2, 38].

Medical reviews have specifically called for quasi-experimental studies [39], approaches that utilize design features to test alternative explanations by increasing control over unmeasured confounding factors [40]. Co-twin control designs, for instance, compare associations between

risks and outcomes among monozygotic and dizygotic twins. The systematic genetic and environmental similarities between twins help to draw conclusions about the mechanisms responsible for the associations found [13, 27, 41]. One co-twin control study suggested that associations between birth weight and cardiovascular disease and stroke may be a result of genetic confounding [27].

Although comparing discordant twins improves internal validity, there are concerns about the external validity of the findings. Birth weight differences in twins may be etiologically distinct from differences in singletons and twins have a greater risk for growth restriction in utero than singletons [42]. Sibling-comparison designs, however, test alternative explanations in a population more generalizable to the public than twins [31] because they account for all genetic and environmental factors that make siblings similar [40, 43]. Few studies, though, have been performed using a sibling-comparison approach [14-16], and they have major limitations. One study predicted blood pressure in a relatively small sample of children [14] while the other only studied associations in males [16]. The third study had excellent follow-up, but used a relatively small sample and predicted a combined cardiovascular outcome that was measured via self-report [15]. All previous sibling-comparison studies were also limited by their sole use of a categorical representation of birth weight or fetal growth. Thus, the field would benefit from research using large datasets and powerful analyses to assess the robustness of associations.

The current investigation sought to rigorously examine the associations between birth weight and mortality and physical morbidity related to cardiovascular disease, stroke, and type 2 diabetes mellitus using one of the most comprehensive, population-based cohorts to date, a Swedish population cohort of over 3.6 million births. We aimed to provide more accurate estimates of the specific associations by using the sibling-comparison design. We also controlled

for measured covariates that varied within families and used both ordinally and continuously measured birth weight.

Materials and Methods

Sample

After approval from the Institutional Review Boards at Karolinska Institutet and Indiana University, a prospective national cohort was created by linking information in the following Swedish registries: (1) Medical Birth Register includes data on more than 99% of all pregnancies in Sweden; (2) Multi-Generation Register contains information about the biological relationships for all individuals living in Sweden; (3) Migration Register contains information on dates of migration in or out of Sweden; (4) Cause of Death Register supplies dates and causes of all deaths; (5) National Patient Register provides diagnoses and dates of all hospital care; (6) National Crime Register includes information about all criminal convictions; and (7) Education Register contains information on the highest level of completed formal education.

The dataset began with 3,619,712 offspring born from 1973 to 2008. We removed multiple births (86,273) and offspring with missing birth weight information (9,888), as well as recorded gestational age values of less than 23 weeks or greater than 42 weeks and 6 days (49,374). Offspring with no sex information (3) and those who had emigrated within the 25 year period (182,223) were removed. We excluded offspring missing maternal identification numbers (158) and invalid parity information (20). The final sample consisted of 3,291,773 offspring born to 1,735,250 distinct biological mothers, representing 90.9% of all recorded Swedish births within the year range investigated. For mortality after one year, a 1 year age criterion was utilized. Therefore, the sub-sample included 3,189,312 offspring born between 1973 and 2007.

For cardiac-related death, hypertension, ischemic heart disease, pulmonary circulation problems, stroke, and diabetes, a 12 year minimum criterion age for diagnosis was used. Therefore, the sub-sample included 2,133,504 offspring born between 1973 and 1995.

Measures

Birth weight

Analyses utilized two different representations of birth weight. For the ordinal representation, birth weight was grouped into the following ranges: ≤ 2500 g, 2501-3000 g, 3001-3500 g, 3501-4000 g (referent), and ≥ 4001 g. Continuously measured birth weight was converted to a linear scale centered at 3750 g (reference 0 point), the approximate mean of the sample.

Offspring outcomes

Two mortality outcomes were predicted. *Mortality after one year* was a right-censored variable that included any death after age one. *Cardiac-related death* was indicated by the primary cause of death being any cardiac-related disease, as identified through International Classification of Disease versions 8, 9, and 10 codes in the Cause of Death Registry; offspring had to have been 12 years old.

We also predicted five physical diseases, as gathered from the National Patient Register, including the first occurrence where the following diagnoses were primary: (1) *hypertension*; (2) *ischemic heart disease*; (3) *pulmonary circulation* problems; (4) *stroke*; and (5) *type 2 diabetes* mellitus. International Classification of Disease codes and further explanation are presented in Appendix Table 1A. Offspring had to be at least 12 years old at the time of diagnosis.

Covariates

The Medical Birth Register provided offspring sex and birth order. Measured maternal and paternal covariates included age at the offspring's birth, highest level of completed education by 2008, and lifetime history of any criminal conviction, which were included to capture some socioeconomic variability in the sample. These covariates were included because they were associated with both birth weight and the outcomes studied.

Analyses

We used Cox survival analysis because of the right-censored outcomes. If offspring did not receive a diagnosis within the study period, they contributed person-time at risk until death, emigration, or the end date of follow-up (December 31, 2009), whichever came first.

We fit a series of four models for each outcome. All models controlled for offspring sex, birth order, and measures of linear and quadratic gestational age. First, we used the ordinal representation of birth weight to estimate clinically-interpretable estimates of risk across outcomes (Model 1). Second, we used a continuous representation of birth weight in a baseline model (Model 2). This model included both a linear and quadratic representation of birth weight. Model fit, established by the Akaike information criterion, was used to determine if linear or quadratic modeling best fit the data for use in adjusted and fixed effects models. Third, we incorporated measured covariates, including offspring-specific (i.e., sex, birth order, and maternal and paternal age at childbearing) and parental-specific covariates (i.e., maternal and paternal highest level of education and history of criminal conviction) (Model 3). Fourth, we fit a fixed effects model that clustered at the maternal level [44], which accounted for factors that siblings share, including all genetic and environmental factors that make siblings similar [43] (Model 4). Siblings were identified as individuals sharing a biological mother (e.g., full or

maternal half-siblings). Covariates that may vary between siblings (i.e. offspring sex and birth order) were controlled for in the fixed effects model.

Sensitivity analyses

We performed sensitivity analyses to examine the role of gestational age and to test assumptions of the sibling-comparison design.

Results

Table 1 presents demographic characteristics by birth weight category. Table 2 presents the number of offspring with all outcomes and Kaplan-Meier product-limit survival estimates for all outcomes.

Mortality

Model 1 utilized ordinal birth weight across the entire cohort population. Figure 1 presents baseline risk estimates (dark bars) with 95% Wald confidence intervals (CI) around the hazard ratio (HR). Point estimates for the reference category, 3501-4000g, are equal to 1. There was a strong inverse association between birth weight (BW) and *mortality after one year* ($HR_{BW: \leq 2500g}$=2.15, 95% CI: 1.97, 2.34) as well as *cardiac-related death* ($HR_{BW: \leq 2500g}$=2.69, 95% CI: 2.05, 3.53).

Model 2 used a continuous representation of birth weight. Associations with the mortality outcomes were better explained by a quadratic model of birth weight (Appendix Table 2A). Figure 1 also presents continuously represented birth weight risk in the baseline quadratic Model 2 (solid black line). Within the figures, it should be noted that a similar interpretation can be drawn from the ordinal bars as from the continuous parameter estimates of Model 2.

The associations remained robust when adjusting for offspring- and parental-specific covariates across mortality outcomes in Model 3. Thus, across outcomes, the associations are independent of offspring sex, birth order, year of birth, maternal and paternal age at childbearing, highest level of education, and history of criminal conviction. Model 3 results are not presented graphically for ease of interpretation.

Finally, Model 4 fitted a fixed effects sibling-comparison model, presented in Figure 1 via the dotted line (continuous) and light grey (ordinal). Consistent with a causal inference, birth weight significantly predicted *mortality after one year* ($HR_{BW: \leq 2500g}$=3.02, 95% CI: 2.52, 3.62) and *cardiac-related death* ($HR_{BW: \leq 2500g}$=4.30, 95% CI: 2.27, 8.14) within differentially exposed siblings while controlling for offspring-specific covariates. Interestingly, across mortality outcomes the magnitudes of association were larger in fixed effect Model 4 than in population estimates for both the ordinal and continuous models. We also identified a similar, though larger in magnitude, pattern of increased risk across models when predicting infant mortality (results available upon request). Parameter estimates for baseline, adjusted, and fixed effects models for the continuously represented birth weight are presented in Appendix Table 3A. Appendix Table 4A presents parameter estimates for ordinal Models 1 and 4 as verification of model specification.

Physical morbidity

Figure 2 presents baseline and fixed effects results for ordinal and continuously measured birth weight across physical morbidity outcomes. There was a strong inverse association between birth weight and *hypertension* ($HR_{BW: \leq 2500g}$=1.58, 95% CI: 1.37, 1.82) present in the population that persisted after adjusting for covariates, and whose magnitude was robust in fixed effects analyses ($HR_{BW: \leq 2500g}$=1.31, 95% CI: 0.92, 1.86). Similarly, there was an inverse association for

ischemic heart disease ($HR_{BW: \leq 2500g}$=2.52, 95% CI: 1.70, 3.73) in the population that was robust across models and remained present in fixed effects analyses ($HR_{BW: \leq 2500g}$=2.18, 95% CI: 0.72, 6.13). *Pulmonary circulation* problems showed an analogous pattern across models (Model 2: $HR_{BW: \leq 2500g}$=1.43, 95% CI: 1.12, 1.83; Model 4: $HR_{BW: \leq 2500g}$=1.41, 95% CI: 0.79, 2.52).

We found an inverse association with *stroke* in the baseline model ($HR_{BW: \leq 2500g}$=1.59, 95% CI: 1.28, 1.96) that was robust in magnitude in the adjusted and fixed effects models ($HR_{BW: \leq 2500g}$=1.37, 95% CI: 0.83, 2.25). The baseline model predicting *type II diabetes* also showed an inverse association where lower birth weight was associated with increased odds ($HR_{BW: \leq 2500g}$=1.79, 95% CI: 1.50, 2.14). This association was also robust in the adjusted model and when using fixed effects modeling ($HR_{BW: \leq 2500g}$=1.71, 95% CI: 1.14, 2.56).

Similar to our mortality results, the magnitudes of association were larger following fixed effects modeling using continuously measured birth weight (Model 4) as compared with magnitudes from population estimates (Models 2 and 3). Parameter estimates for baseline, adjusted, and fixed effects models for the continuously represented birth weight are presented in Appendix Table 3A while ordinal parameter estimates Models 1 and 4 are presented in Appendix Table 4A for model specification verification.

Sensitivity analyses

First we tested if gestational age influenced the results. In particular, we limited the cohort to full term (≥ 37 weeks) births and found that results were not biased by premature births (Appendix Figure 1A), though the reduced number of individuals at the lowest birth weights born full term contributed to large confidence intervals around these estimates. In addition, although the sample has been shown to have reliable gestational ages whether measured via last menses or ultrasound [45], we examined if the removal of extreme gestational ages (< 23 weeks

and ≥ 42 weeks and 6 days) affected the results by performing an analysis that included all of the individuals, regardless of their gestational age. The results gave commensurate interpretations to the main analyses and sensitivity analyses limiting the sample to full term births only (results available upon request). Second, we tested an assumption of the sibling-comparison design by exploring if results from families with more than one offspring would generalize to offspring without siblings. The results suggested that estimates were not biased by differences between families with only one offspring and those with more than one offspring (Appendix Figure 2A).

Discussion

After rigorous, quasi-experimental testing via sibling-comparisons in one of the largest population databases to date, we found that risks associated with low birth weight influence subsequent mortality and morbidity related to cardiovascular disease, stroke, and type 2 diabetes. Thus, results underscore the importance of birth weight as a risk factor for subsequent mortality and morbidity and findings are consistent with the Developmental Origins of Health and Disease hypotheses [1, 5, 7, 12, 22]. Further, we found that the risk for studied outcomes increases continuously as birth weight decreases, even for those infants born within the normal (>2500g) range.

Our findings support previous non-quasi-experimental studies showing increased risk for all-cause mortality and cardiac-related mortality [4]. After controlling for similarities between siblings, the associations between birth weight and mortality outcomes were robust. In fact, the estimates of risk slightly increased in magnitude from the population estimates. Previous studies on birth weight have also found increases in magnitude after fitting a fixed effect sibling-comparison model [16]. Sensitivity analyses limiting the sample to families with only one

offspring suggested that the increased magnitudes of association were not due to a bias of higher estimates in families with more than one offspring. Controlling for stable maternal characteristics when using a fixed effects model, such as maternal body size, may have allowed the offspring-specific risk to emerge.

Similarly, our morbidity results showed inverse associations with birth weight across all outcomes and the associations were robust in sibling-comparison designs. In particular, our results support positive associations between birth weight and hypertension found in meta-analyses [11, 17] and previous sibling-comparison studies [14-16]. We also found an inverse association between birth weight and pulmonary circulation problems. Though the younger age range in our study may be a limitation, our findings are in agreement with previous research predicting blood pressure in children [14]. Magnitudes of association were slightly elevated in sibling-comparison models as seen in with continuous representation of birth weight figures (Figure 2). This supports previous research [14, 16] and may be indicative of controlling for stable maternal characteristics.

When predicting ischemic heart disease, our findings agree with several previous epidemiological studies [5-10] suggesting that low birth weight is associated with increased risk for cardiovascular disease. While our results agree with dizygotic twin comparisons, our results are in contrast with monozygotic twin comparisons that suggest that associations are confounded by shared genetic factors [27]. Similarly, when predicting type 2 diabetes and stroke, our results agree with a previous meta-analysis [18], epidemiological studies [15, 19], and dizygotic twin comparisons [27, 31, 41]. Previous monozygotic twin comparisons, however, have suggested that genetic confounding may be responsible for the associations identified [27, 31, 41]. Our findings also disagree with a previous sibling-comparison study on type 2 diabetes, though the

authors point out that this finding may have been limited by a small sample size [15]. Thus, our sibling-comparison results provide unique converging evidence with previous dizygotic twin comparisons and previous traditional epidemiological studies while also offering improved generalizability and external validity when studying birth weight [31, 42]. Future research utilizing different quasi-experimental designs, each with their own assumptions and limitations, will further clarify the associations [46].

Identifying the mediating mechanisms underpinning these associations is complex, as low birth weight may be a marker of a variety of prenatal [47] or preconception [48] insults. Epigenetic processes, including DNA methylation and histone modification, have been proposed as mechanisms underlying associations between low birth weight and the studied outcomes [20-22]. Prenatal cues, such as imbalanced maternal nutrition or stress [20, 21, 49], induce shifts in structural and functional fetal development that may reduce birth weight, towards a phenotype best matched to the prenatal condition or the predicted postnatal environment [22]. If an environmental mismatch occurs, the developmental phenotype established inside the womb may contribute to various diseases via metabolic set-point miss-adaptation [20, 22, 50]. For example, the combination of impaired fetal growth and rapid childhood weight gain is associated with increased risk for adult cardiovascular disease [9, 20, 50, 51].

The conclusions from the current project are bolstered by several strengths. First, our study combined features designed to minimize the influence of confounding factors shared by siblings with statistical control for measured covariates to help rule out plausible alternative hypotheses. The sibling-comparison results arguably are more generalizable to the general population than co-twin control studies, because of the inherent problems in using twins to study birth weight. Further, we performed a sensitivity analysis comparing outcomes between

offspring with siblings and those without. These analyses tested assumptions of the sibling-comparison approach, examined if the data used in fixed effects models were biased, and suggested that results are generalizable to families without multiple children. Second, we utilized a comprehensive, population-based dataset to test associations across a broad range of mortality and physical morbidity outcomes, which provided the opportunity to find converging evidence. Additionally, our outcomes were physician-diagnosed diseases, supporting measurement validity and the external validity of our conclusions. Third, our predictor was birth weight, but all associations were adjusted for gestational age at birth. We also verified ordinally measured birth weight findings with continuously measured birth weight and were thus able to increase statistical power while examining the full continuum of birth weight. In addition, we performed a sensitivity analysis limiting the sample to full-term births only, as well as a sensitivity analysis including all gestational ages, both of which provided further evidence of the robustness of the findings.

Despite these strengths, several limitations must be considered and addressed in future research. First, sibling-comparisons are not randomized controlled studies; therefore, we could not rule out all possible confounding factors and causation cannot be shown. Our findings only support the Developmental Origins hypothesis; they do not prove it. While genetic factors that make siblings similar is addressed in the design, offspring-specific genetic factors that influence birth weight cannot be accounted for [46] and may be driving the associations identified. Second, fixed effects models have lower statistical power than population-based estimates, but we addressed this by utilizing continuously measured birth weight. In the future, using other quasi-experimental approaches with different assumptions and limitations may clarify associations further [40]. In particular, future sibling-comparison studies could compare the estimates in full-

and maternal half-siblings to further explore the possibilities of genetic confounding [46]. Unfortunately, the sample size in the current study was not large enough to make meaningful comparisons of these types of siblings. Third, replication in countries with different health care availability and socioeconomic diversity is needed. Fourth, an examination using data with a longer follow-up period would help to determine if risk is mainly captured by relatively early-onset outcomes. Finally, future work should also examine the offspring's later life risk factors and/or body composition.

Overall, the current results emphasize the importance of considering birth weight as a risk factor for mortality and cardiovascular-related, stroke, and type 2 diabetes outcomes. As such, the findings are consistent with the Developmental Origins of Health and Disease hypothesis. While increasing birth weight may not be an efficient or feasible means of prevention [11, 28], the current results support the need for future research focused on elucidating the mechanisms linking birth weight with mortality and morbidity [2].

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Table 1. Demographic characteristics of 3,291,773 Offspring Born 1973-2008 in Sweden.

Characteristic	Birth Year	Birth Weight Category, g														
		≤ 2,500 (*n* = 114,580)			2,501-3,000 (*n* = 366,500)			3,001-3,500 (*n* = 1,075,447)			3,501-4,000 (*n* = 1,152,337)			≥ 4,000 (*n* = 583,909)		
		No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Offspring (*n* = 3,291, 773)	1973-2008															
Female		58,657	51.19		207,481	56.61		573,332	53.31		533,202	46.27		220,119	37.76	
Gestational age, days				245.46 (25.53)			271.19 (12.10)			278.14 (9.41)			282.14 (8.27)			285.24 (7.77)
Maternal (*n* = 1,732,107)	1924-1995															
Age at birth, years				28.85 (5.67)			28.43 (5.36)			28.59 (5.19)			28.96 (5.10)			29.55 (5.06)
Swedish nationality		54,045	83.77		169,706	83.00		491,255	84.77		518,302	87.12		254,761	88.68	
Secondary education, 3 years		31,870	49.35		105,639	51.62		323,120	55.71		347,214	58.32		170,492	59.31	
Adult severe psychopathology		1,748	2.71		4,493	2.20		10,606	1.83		9,629	1.62		4,377	1.52	
Criminality		8,939	13.84		26,443	12.92		65,981	11.38		61,356	10.31		28,207	9.81	
Paternal (*n* = 1,725,359)	1904-1993															
Age at birth, years				31.75 (6.55)			31.38 (6.28)			31.49 (6.07)			31.78 (5.96)			32.28 (5.91)
Swedish nationality		52,049	83.61		165,781	82.69		485,000	84.50		518,434	87.04		259,048	89.02	
Secondary education, 3 years		27,192	43.63		90,199	44.92		274,812	47.82		294,778	49.44		145,192	49.84	
Adult severe psychopathology		1,345	2.16		4,033	2.01		10,059	1.75		9,399	1.58		4,172	1.43	
Criminality		25,953	41.64		81,223	40.45		219,628	38.22		216,353	36.28		101,834	34.96	

Abbreviations: No., number of individuals by birth weight group; SD, standard deviation; %, percentage of individuals by birth weight group, for offspring, the total number by birth weight group is listed in the column header, for mother and father variables, the total number of distinct mothers and fathers are listed in the left column and percentages are based on the number of non-missing cases for each variable.

Table 2. Mortality and Physical Morbidity Outcomes by Birth Weight of Offspring Born 1973-2007 in Sweden.

			Birth Weight Category, g									
	Birth Year	Total No. of Persons	≤ 2,500 (*n* = 114,580)		2,501-3,000 (*n* = 366,500)		3,001-3,500 (*n* = 1,075,447)		3,501-4,000 (*n* = 1,152,337)		≥ 4,000 (*n* = 583,909)	
Outcome			**No.**	**KM est.**	**No.**	**KM est.**	**No.**	**KM est.**	**No.**	**KM est.**	**No.**	**KM est.**
Mortality												
Died after 1st year	1973-2007	3,189,312	832	0.01	1,630	0.01	3,712	0.01	3,704	0.01	1,892	0.01
Cardiac-related death	1973-1995	2,133,504	499	0.44	462	0.13	850	0.08	760	0.07	383	0.07
Physical Morbidity												
Hypertension	1973-1995	1,182,992	438	0.38	1,015	0.28	2,350	0.22	1,992	0.17	965	0.17
Ischemic heart disease	1973-1995	1,423,777	63	0.05	153	0.04	264	0.02	286	0.02	132	0.02
Pulmonary circulation	1973-1995	200,103	331	0.29	457	0.12	881	0.08	802	0.07	364	0.06
Stoke	1973-1995	1,018,885	322	0.28	620	0.17	1,359	0.13	1,319	0.11	705	0.12
Type 2 diabetes	1973-1995	770,096	780	0.68	2,532	0.69	6,811	0.63	7,275	0.63	3,734	0.64

Abbreviations: No., number of individuals by birth weight group; KM est., Kaplan Meier product-limit survival estimate at 25 (Died after 1st year only) and 35 years of age. Kaplan-Meier estimates present the probability of the occurrence of an event at any point in time. Estimates are calculated by the number of participants surviving, or those who have not received a diagnosis, divided by the number of participants still at risk (i.e., not censored). Total probability of surviving until the indicated age is then calculated by multiplying all probabilities of survival at all preceding time intervals. The survival probabilities are then multiplied by 100 to get a percentage.

Figure Legend.

Figure 1. Associations from continuous (line) and ordinal (bar with 95% confidence intervals) representation of birth weight when predicting mortality outcomes in offspring born between 1973-2007 (A: death after 1st year) and 1973-1995 (B: cardiac-related death) in Sweden. Baseline, population-wide estimates are shown via the solid line and dark bars. Sibling-comparison, fixed effects models are shown via dotted lines and light bars.

Figure 2. Associations from continuous (line) and ordinal (bar with 95% confidence intervals) representation of birth weight when predicting (A) hypertension, (B) ischemic heart disease, (C) pulmonary circulation, (D) stroke, and (E) type 2 diabetes in offspring born between 1973-1995 in Sweden. Baseline, population-wide estimates are shown via the solid line and dark bars. Sibling-comparison, fixed effects models are shown via dotted lines and light bars.

Figure 1.

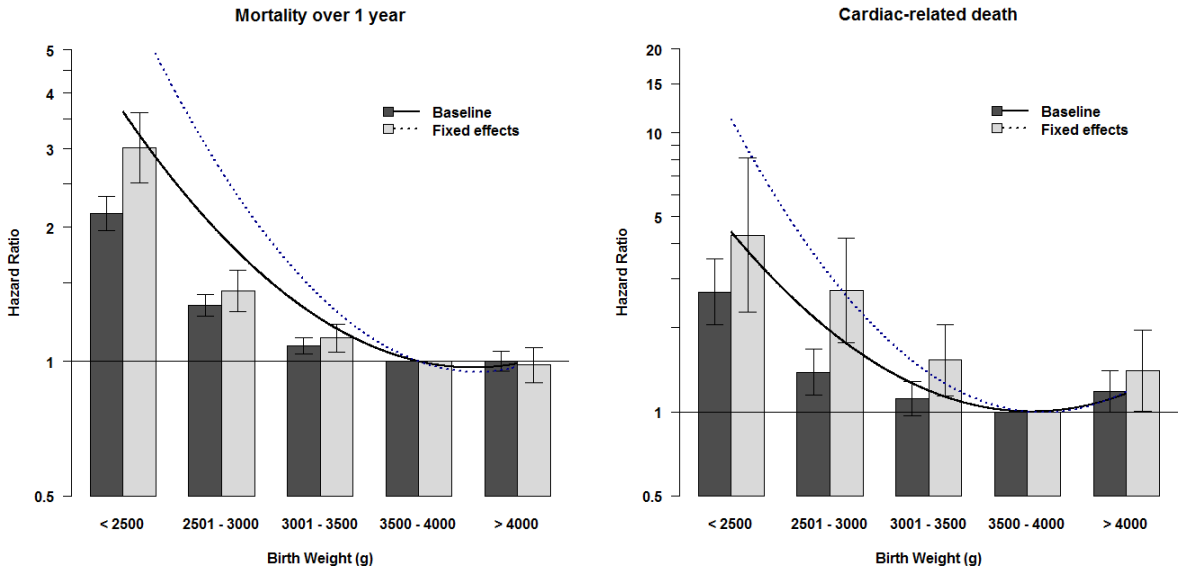

Mortality over 1 year
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)
Cardiac-related death
Hazard Ratio
20
15
10
5
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

Figure 2.

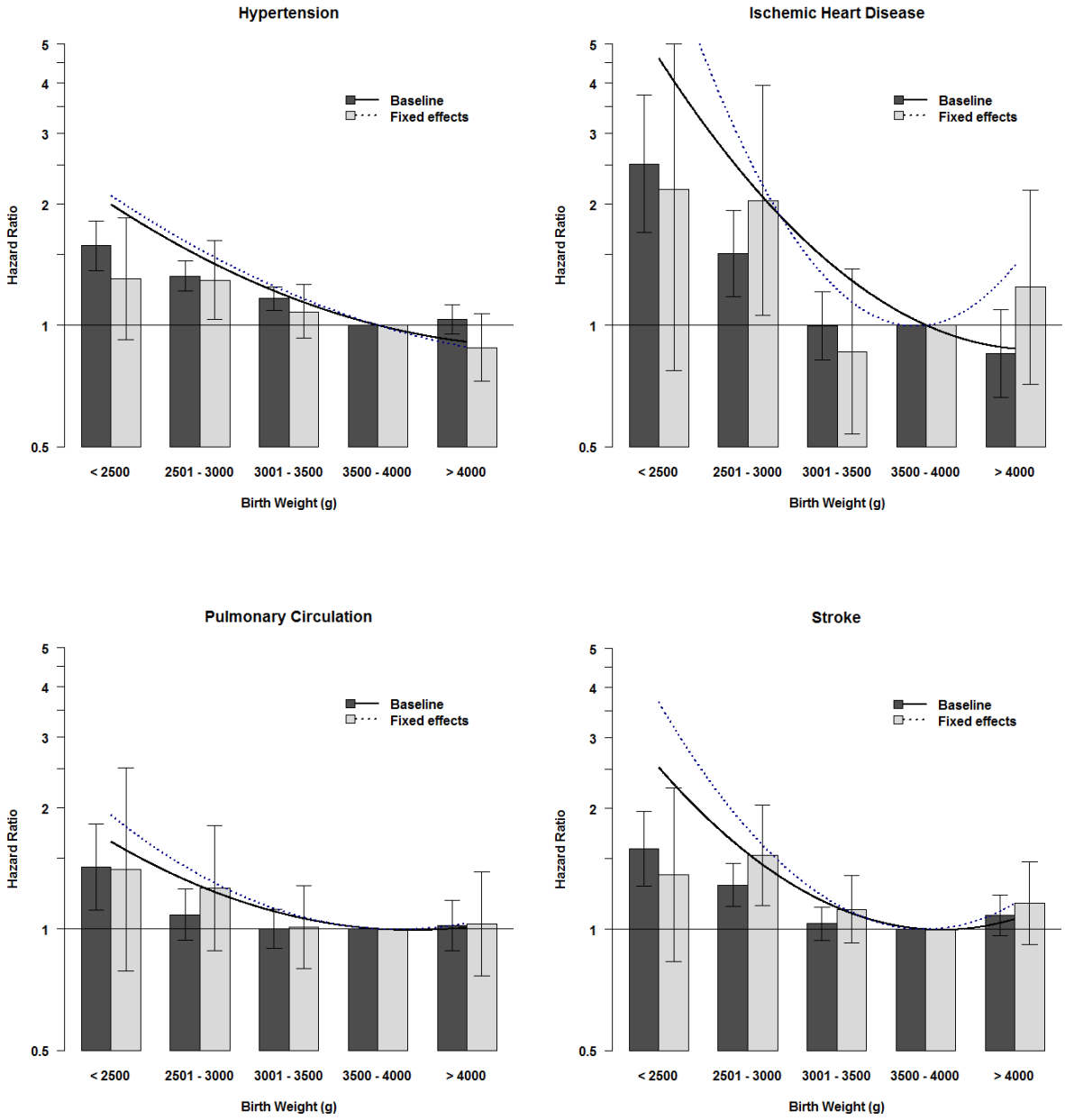
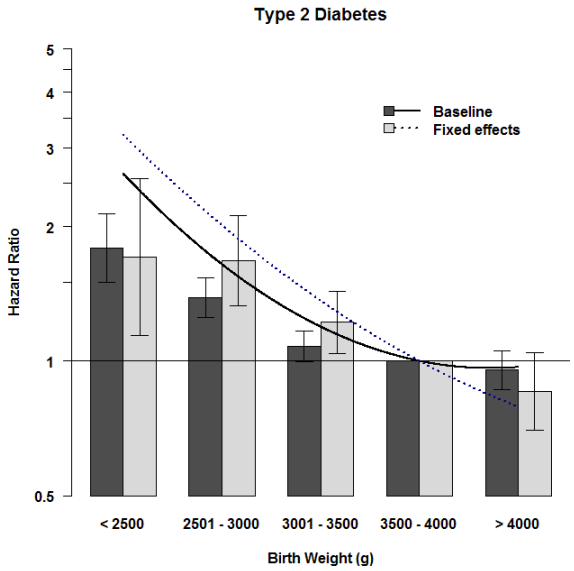

Hypertension
Ischemic Heart Disease
Pulmonary Circulation
Stroke
Baseline
Fixed effects
Hazard Ratio
5
4
3
2
1
0.5
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

Figure 2 cont.



Appendix: Birth weight, physical morbidity, and mortality: A population-based sibling-comparison study

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Table 1A. International Classification of Disease code used to classify outcomes with outcome description.

Outcome	Data Source Register	International Classification of Disease Version	Codes	Description
Mortality Outcomes				
Mortality after one year	Cause of Death	--	--	Death after the first year of postnatal life due to any cause
Cardiac-related death	Cause of Death	8, 9, 10	All below plus 420-425, 427-429, 440-448, I30-I52, I70-I79	Death due to cardiac or diabetic related occurrence including all below and others
Physical Morbidity Outcomes				
Hypertension	HD	8, 9, 10	401-405, I10-I15	Essential, secondary, and hypertensive disease of the heart and kidney
Ischemic heart disease	HD	8, 9, 10	410-414, I20-I25	Acute and other myocardial infarction, angina pectoris, other forms of chronic ischemic heart disease including atherosclerotic heart disease and aneurysm of the heart
Pulmonary circulation problems	HD	8, 9, 10	415-417, 426, 450, I26-I28	Acute pulmonary heart disease, primary pulmonary hypertension, other diseases of pulmonary circulation
Stroke	HD	8, 9, 10	430-438, I60-I69	Subarachnoid, intracerebral, and other intracranial hemorrhage, occlusion and stenosis of precerebral and cerebral arteries, transient cerebral ischemia, acute, other, and ill-defined cerebrovascular disease, late effects of cerebrovascular disease
Type 2 Diabetes Mellitus	HD	8, 9, 10	250 (except .x1 and .x3), E11-E14	Type 2 diabetes mellitus

Note: HD = Hospital Discharge

Table 2A. Comparison of fit indices across baseline linear and quadratic baseline models for model selection.

Table 2A. Comparison of Akaike information criterion (AIC) values for linear and quadratic candidate baseline models.

Outcome	Candidate Baseline Model: Linear Birth Weight	Candidate Baseline Model: with Quadratic Birth Weight	AIC-min	ΔAIC
Mortality				
Died After 1st Year	407651.93	407512.95	L + Q	138.98
Cardiac-related Death	84485.01	84365.65	L + Q	119.36
Physical Morbidity				
Hypertension	182314.86	182302.94	L + Q	11.92
Ischemic Heart Disease	24605.82	24599.80	L + Q	6.02
Pulmonary Circulation	78602.59	78539.61	L + Q	62.98
Stroke	121898.24	121855.48	L + Q	42.76
Type 2 Diabetes Mellitus	608347.78	608346.83	L + Q	0.95

Notes: L + Q = baseline model with both linear and quadratic birth weight

The model selection table compares the Akaike information criterion (AIC) for the baseline model with linear (L) birth weight only and the baseline model with both linear and quadratic (L+Q) birth weight. The column labeled "AIC-min" indicates which of the two candidate models (L or L+Q) yielded the lowest AIC. The observed difference, $\Delta AIC = AIC_L - AIC_{L+Q}$, provides a measure of relative merit that is free of scaling constants and can be interpreted as strength of evidence for model selection purposes [52].

Table 3A. Comparison of the unstandardized linear and quadratic regression coefficients for the baseline, adjusted, and fixed effects models.

Table 3A. Comparison of the unstandardized linear and quadratic regression coefficients for the baseline, adjusted, and fixed effects models.

	Baseline (Model 2)				Adjusted (Model 3)				Fixed Effects (Model 4)			
	Linear term		Quadratic term		Linear term		Quadratic term		Linear term		Quadratic term	
Outcomes	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**
Mortality												
Died After 1st Year	**-0.039**	0.005	**0.012**	0.001	**-0.025**	0.005	**0.012**	0.001	**-0.061**	0.011	**0.017**	0.002
Cardiac-related Death	-0.004	0.016	**0.018**	0.003	0.004	0.016	**0.018**	0.003	-0.026	0.040	**0.027**	0.008
Physical Morbidity												
Hypertension	**-0.043**	0.008	**0.004**	0.002	**-0.039**	0.008	**0.004**	0.002	**-0.052**	0.024	0.003	0.004
Ischemic Heart Disease	**-0.076**	0.025	**0.010**	0.004	**-0.070**	0.025	**0.011**	0.004	0.024	0.074	**0.031**	0.013
Pulmonary Circulation	-0.012	0.014	0.005	0.003	-0.006	0.014	0.005	0.003	-0.009	0.036	0.007	0.006
Stroke	-0.011	0.011	**0.010**	0.002	-0.005	0.011	**0.011**	0.002	0.001	0.029	**0.016**	0.005
Type 2 Diabetes Mellitus	**-0.035**	0.010	**0.008**	0.002	**-0.025**	0.010	**0.008**	0.002	**-0.091**	0.024	0.004	0.005

Notes: b = maximum likelihood estimate of the unstandardized regression coefficient; SE = estimated standard error; Highlighted coefficients have a p-value > 0.05.

Table 4A. Parameter estimates of baseline and fixed effects models using ordinal representation of birth weight.

Web Table 4 presents the unstandardized regression coefficients with standard errors and the Hazard Ratio parameter estimates with 95% confidence intervals associated with the ordinal bins of birth weight across baseline and fixed effects models. The baseline estimates presented here correspond with the point estimates presented in Figures 1 and 2 within the main paper.

Estimates for fixed effects models using ordinal representation of birth weight provide a comparison analysis to examine the sibling comparison results absent of assumptions about the underlying pattern (i.e., linear or quadratic) of the associations between birth weight and the indices of mortality and morbidity. Figures 1 and 2 in the main paper provide a graphical comparison of the baseline and fixed effects models using ordinally represented birth weight. The fixed effects results using ordinal representation of birth weight give commensurate results with analyses based on linear and quadratic modeling presented in the main analyses. It can be noted, however, that the confidence intervals around fixed effects estimates using ordinal bins are larger than those presented in the main analyses due to the reduced statistical power in moving from a continuous representation of birth weight to ordinal bins. These results suggest that assumptions about the shape of model fitting using families with multiple offspring (which are the only informative families for the sibling-comparison estimates) do not account for the fixed effects results using the continuous index of birth weight.

Table 4A. Cox hazard regression parameter estimates for baseline and fixed effects models using ordinal birth weight.

Outcome	Model	Birth Weight (g)	1973-1995 B	SE	HR	95%LCL	95%UCL
Mortality							
Died After 1st Year	**Baseline**	**≤ 2500**	0.764	0.045	2.146	1.966	2.343
		2501-3000	0.291	0.029	1.338	1.265	1.415
		3001-3500	0.080	0.021	1.084	1.039	1.130
		≥ 4001	**0.003**	0.026	**1.003**	0.954	1.056
	Fixed effects	**≤ 2500**	1.104	0.093	3.016	2.515	3.618
		2501-3000	0.364	0.055	1.439	1.292	1.603
		3001-3500	0.121	0.038	1.129	1.048	1.215
		≥ 4001	**-0.018**	0.046	**0.983**	0.898	1.076
Cardiac-related Death	**Baseline**	**≤ 2500**	0.988	0.139	2.686	2.046	3.526
		2501-3000	0.326	0.096	1.385	1.148	1.672
		3001-3500	**0.106**	0.073	**1.112**	0.964	1.283
		≥ 4001	0.168	0.086	**1.183**	0.999	1.402
	Fixed effects	**≤ 2500**	1.459	0.325	4.302	2.274	8.139
		2501-3000	1.003	0.220	2.725	1.771	4.193
		3001-3500	0.428	0.150	1.533	1.143	2.057
		≥ 4001	0.340	0.172	1.404	1.002	1.969
Physical Morbidity							
Hypertension	**Baseline**	**≤ 2500**	0.456	0.073	1.578	1.368	1.821
		2501-3000	0.282	0.044	1.326	1.217	1.445
		3001-3500	0.153	0.033	1.166	1.092	1.244
		≥ 4001	**0.033**	0.043	**1.033**	0.950	1.124
	Fixed effects	**≤ 2500**	**0.268**	0.178	**1.308**	0.922	1.855
		2501-3000	0.259	0.115	1.296	1.035	1.624
		3001-3500	**0.079**	0.078	**1.082**	0.929	1.262
		≥ 4001	**-0.127**	0.099	**0.881**	0.726	1.069
Ischemic Heart Disease	**Baseline**	**≤ 2500**	0.925	0.200	2.521	1.703	3.733
		2501-3000	0.409	0.126	1.506	1.177	1.927
		3001-3500	**-0.003**	0.099	**0.997**	0.820	1.212
		≥ 4001	**-0.161**	0.128	**0.851**	0.662	1.095
	Fixed effects	**≤ 2500**	**0.777**	0.529	**2.176**	0.772	6.132
		2501-3000	0.714	0.335	2.043	1.059	3.941
		3001-3500	**-0.149**	0.241	**0.861**	0.537	1.381
		≥ 4001	**0.219**	0.284	**1.245**	0.713	2.172
Pulmonary Circulation	**Baseline**	**≤ 2500**	0.357	0.126	1.429	1.116	1.829
		2501-3000	**0.082**	0.075	**1.085**	0.937	1.258
		3001-3500	**0.002**	0.056	**1.002**	0.898	1.118
		≥ 4001	**0.022**	0.073	**1.022**	0.886	1.178

Figure 1A. Baseline and fixed effects parameter estimates when limiting sample to full term births only.

Compared with parameter estimates from the main analyses (left column) which included all gestational ages, results from analyses limited to full term births did not substantially alter the results (right column). This suggests that associations presented in main analyses were not biased by extremely premature or late births. The one exception may be found for type 2 diabetes mellitus; parameters corresponding to the smallest ordinal category of birth weight were attenuated as compared with main analyses though small sample size may have contributed to this attenuation.

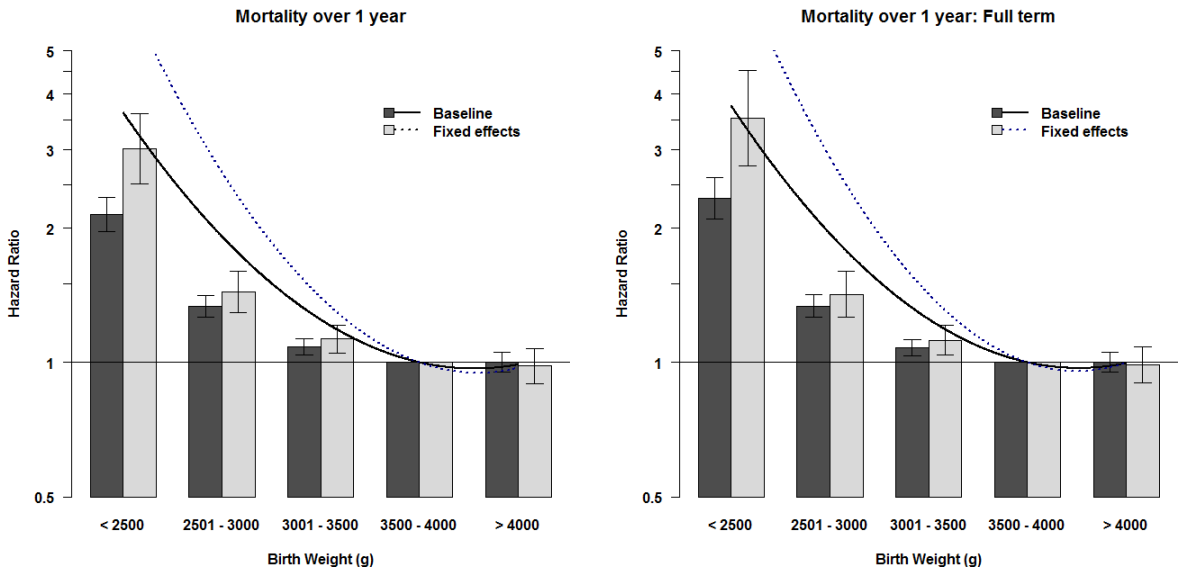


Figure 1A cont.

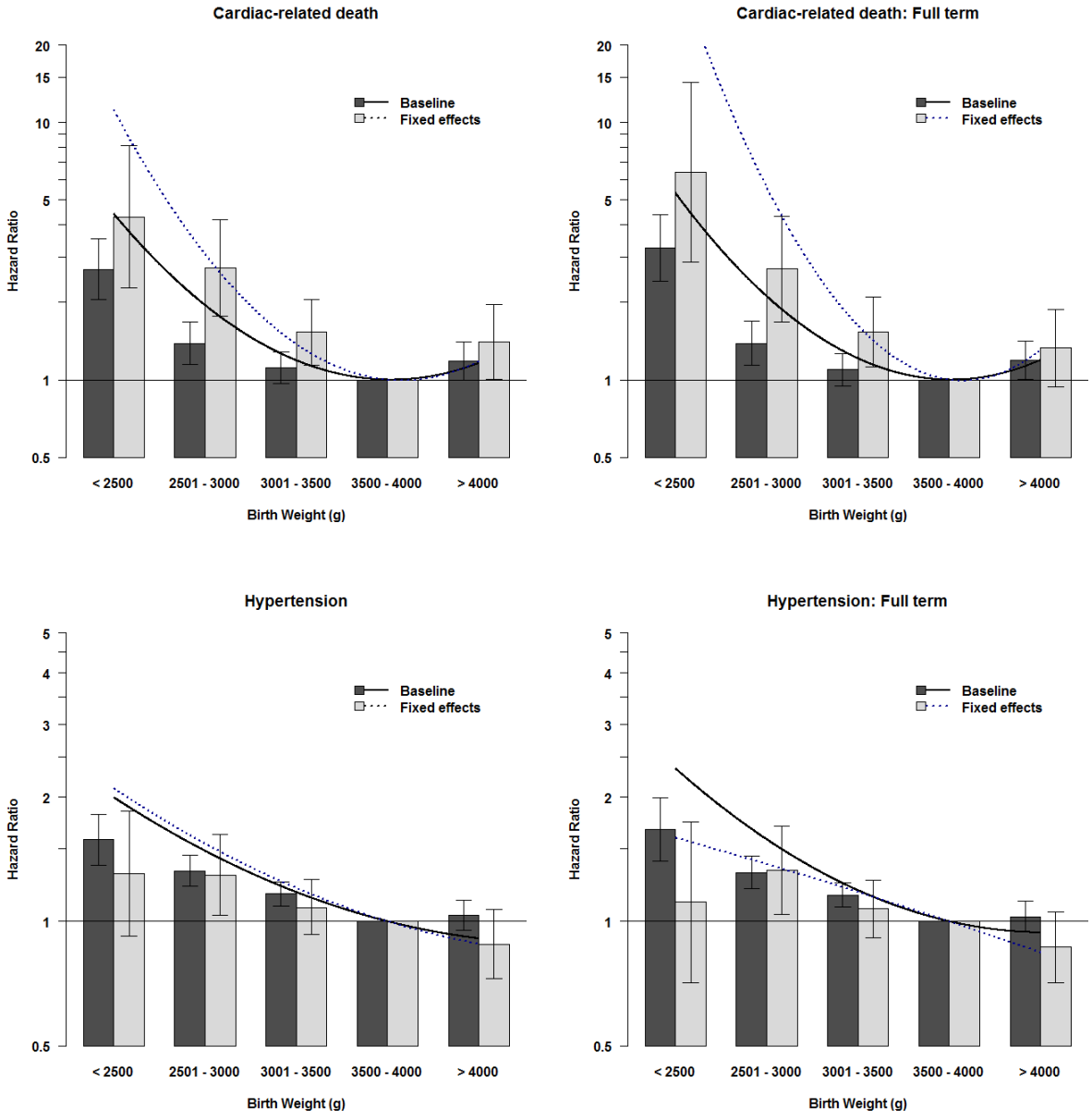


Figure 1A cont.

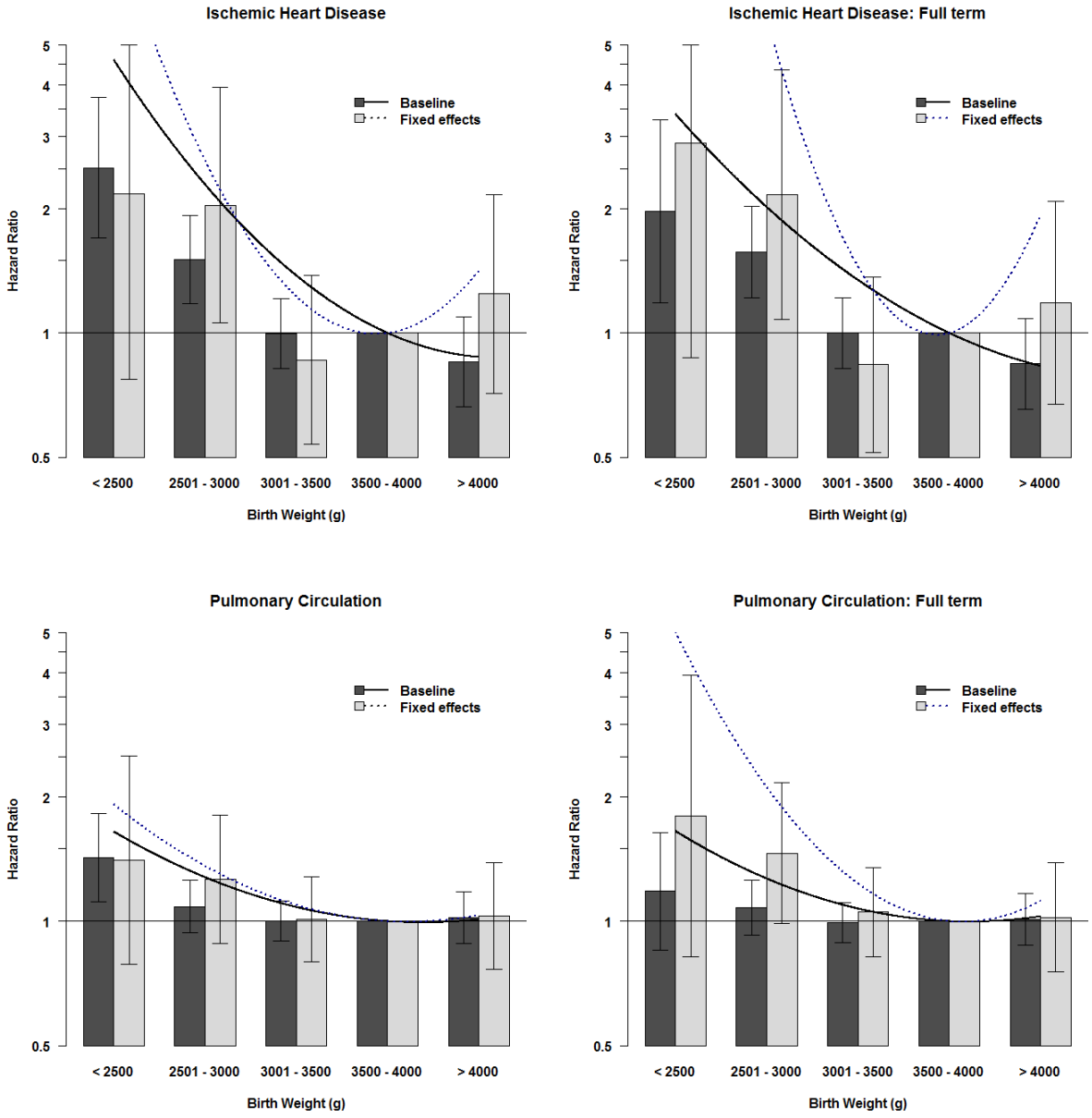


Figure 1A cont.

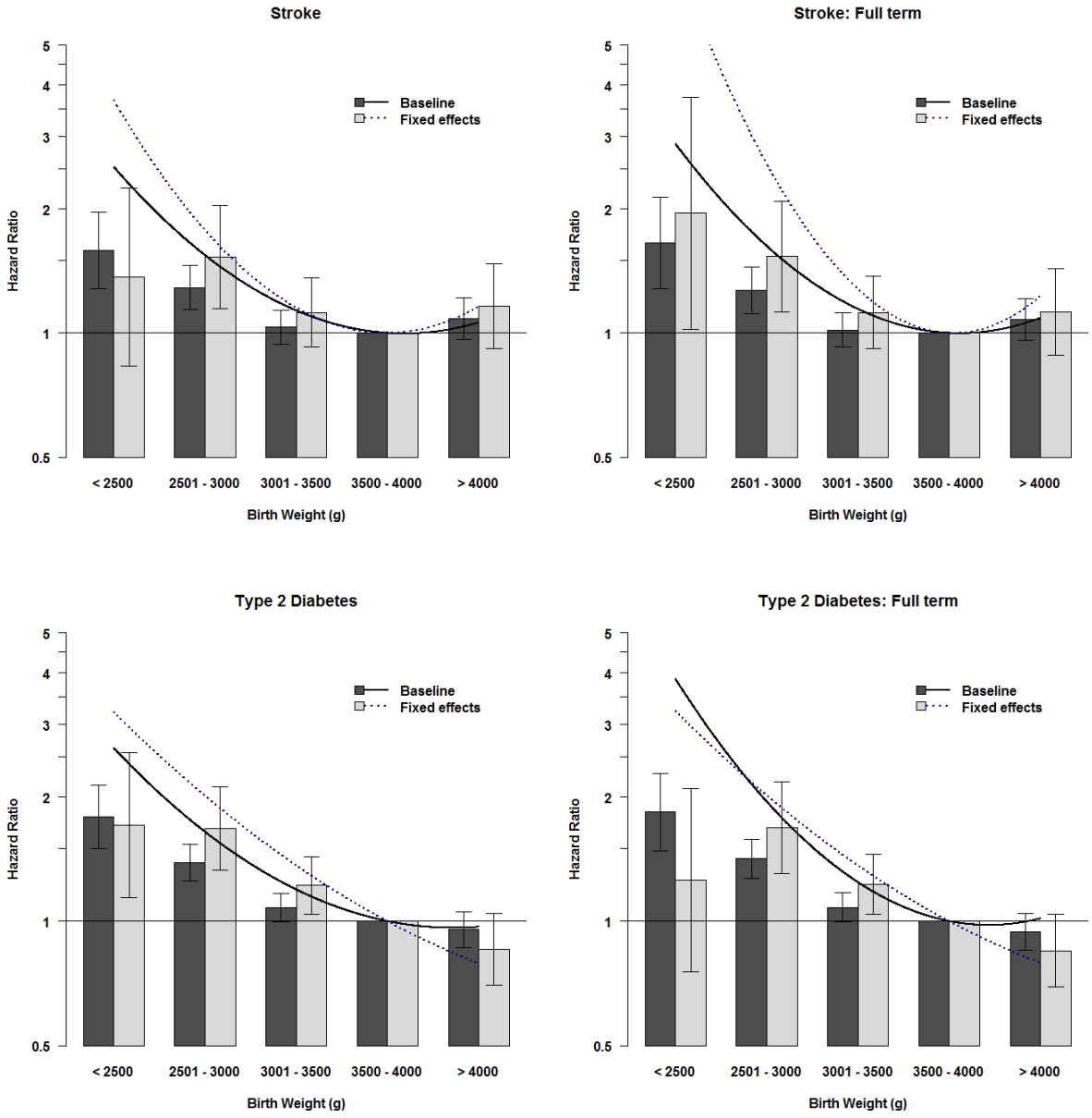


Figure 2A. Comparison of the baseline model association between birth weight and offspring outcomes estimated separately for (a) offspring from families with more than one child and (b) offspring from families with only one child.

Sibling-comparison studies assume that findings from families with multiple offspring generalize to families with only one offspring. The interpretation of the sibling-comparison results could be confounded if the population-based associations were different in offspring who had siblings than in those that are only children. If systematic magnitude differences are found between offspring with siblings and only children, then the reduction or increase in association magnitude found in the fixed effects models may be due to alternate explanations.

To help assess whether a bias was introduced by analyzing families with multiple offspring, we estimated the population-based estimates between birth weight and offspring outcomes in (a) offspring without siblings and (b) offspring with siblings. Each figure below presents these two baseline models. One model (dark bars with 95% confidence intervals) estimated on the sub-sample of offspring from families with only one offspring within the dataset. The second model (light bars with 95% confidence intervals) was estimated on the sub-sample of offspring from families with more than one child.

The figures show that the baseline associations are largely comparable for the two sub-samples of offspring. The figures also suggest that differences between the sub-samples do not account for differences in the sibling-comparison estimates as compared with the population estimates presented in the main paper. Across outcomes, associations in the two sub-samples are in the same direction and the magnitudes of association greatly overlap. Where the magnitudes differ between sub-samples, birth weights were lowest and therefore the sample sizes were the smallest. Additionally, we found no pattern where magnitudes were always larger in one sub-sample. Overall, this sensitivity analysis suggests that the sibling-comparison results that showed changes in magnitude from the population analyses are not due to different population-based estimates in offspring with siblings than in offspring who are only children.

Figure 2A cont.

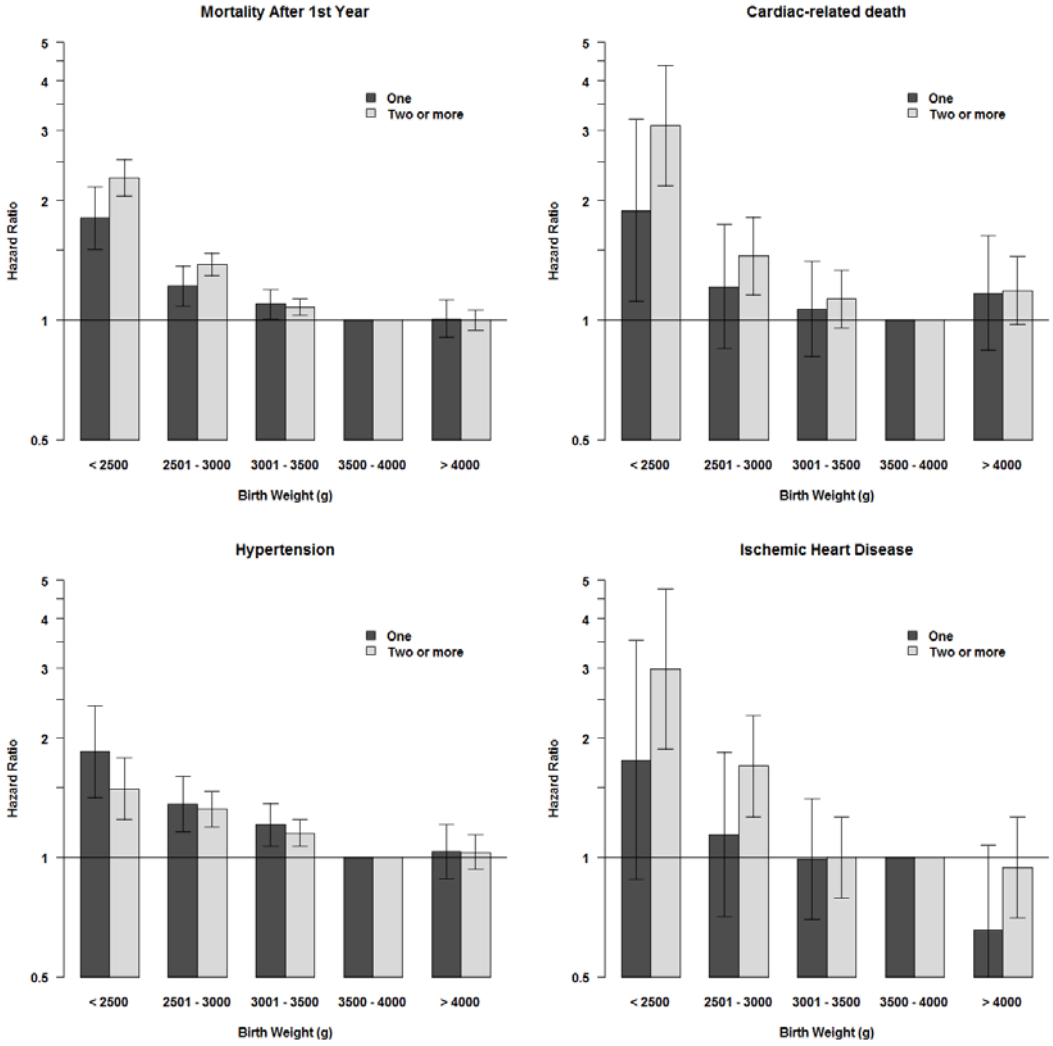
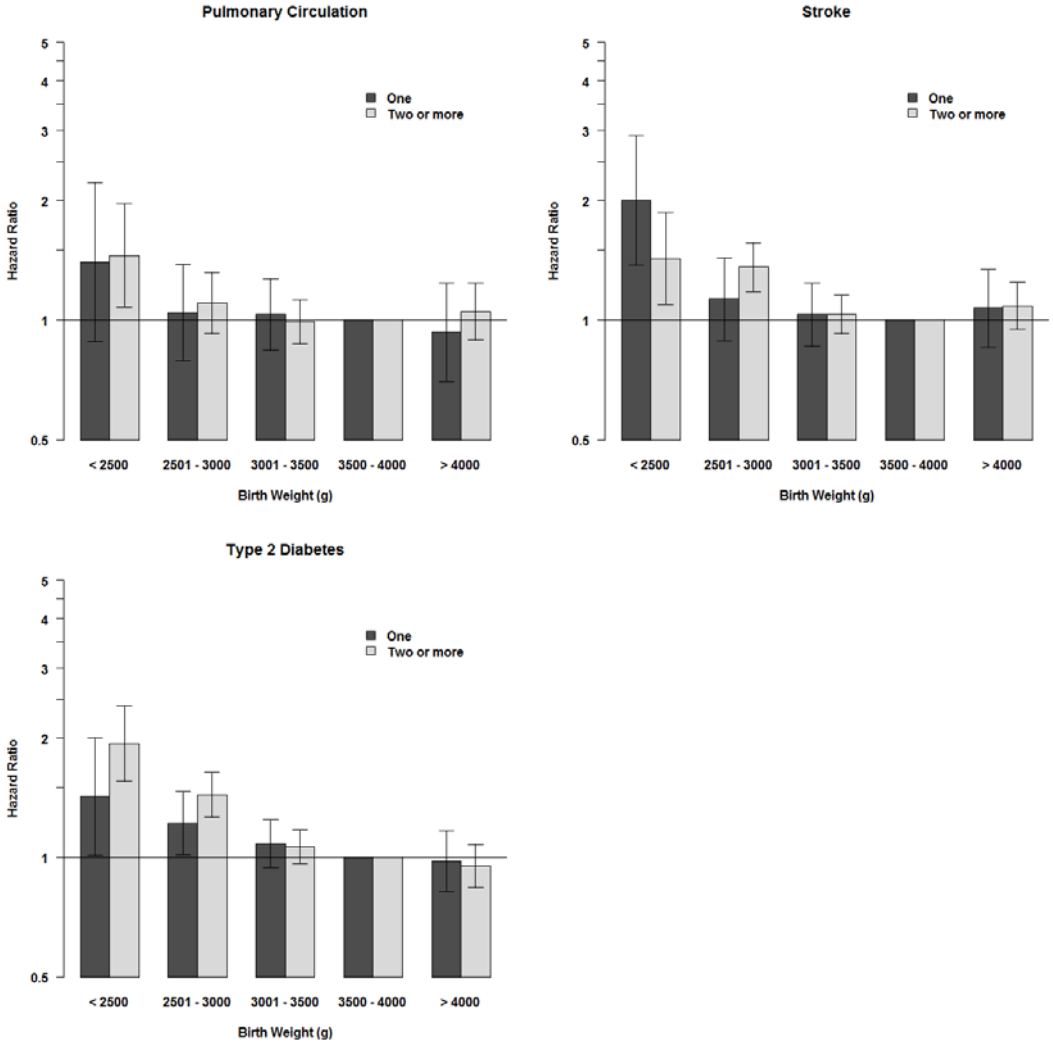


Figure 2A cont.



2.4 Fetal growth and psychiatric and socioeconomic problems: A population-based sibling-comparison

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Abstract

Background: It is unclear if associations between fetal growth and psychiatric and socioeconomic problems are consistent with causal mechanisms.

Aims: To estimate the extent to which associations are due to unmeasured confounding factors using a sibling-comparison approach.

Methods: We predicted outcomes from continuously measured birth weight in a Swedish population cohort (n=3,291,773), while controlling for measured and unmeasured confounding.

Results: In the population, lower birth weight (e.g., <2500g) increased the risk of all outcomes. Sibling-comparison models indicated that lower birth weight independently predicted increased risk for autism spectrum disorder (e.g., $HR_{BW: \leq 2500g}$=2.44, 95% CI=1.99-2.97) and attention deficit hyperactivity disorder. Though attenuated, associations remained for psychotic or bipolar disorder and educational problems. Associations with suicide attempt, substance use problem, and social welfare receipt, however, were fully attenuated in sibling-comparisons.

Conclusions: Results suggest that fetal growth, and factors that influence it, contribute to psychiatric and socioeconomic problems.

Declaration of interest: None.

Indicators of poor fetal growth, such as low birth weight (≤2500 g), are linked with increased offspring risk for neurodevelopmental disorders [1-4], academic problems [5-8], and poor social outcomes [5]. The Developmental Origins of Health and Disease hypothesis, which puts forth that developmental plasticity contributes to fetal physiological adaptations made in response to the intrauterine environment, has been used to explain the identified associations [9]. The mechanisms linking fetal growth with later psychiatric, academic, and social problems are not straightforward, however. Impaired fetal growth may act as an independent, environmental risk factor, as twin studies have shown for attention-deficit hyperactivity disorder (ADHD) [10-12]. Previously identified associations may also be due to unmeasured selection factors, such as environmental confounding or shared genetic liability, that influence both the likelihood of experiencing the risk and the outcome [13, 14]. For example, low birth weight is associated with environmental risks that are themselves predictive of subsequent adverse outcomes [15], and family and twin studies indicate that genetic and shared environmental factors influence birth weight [16]. As such, the field should remain cautious in drawing causal conclusions between fetal growth and these outcomes. Conflicting results across outcomes also have been found [1, 5, 17-20], and, in fact, a recent meta-analysis showed that associations between low birth weight and depression may be due to publication bias [19]. Further, previous studies have been limited by self- and parent-report of both risk and outcome [1, 21]. Thus, analyses that determine precise and accurate estimates of the strength of the associations, as well as those that begin to pull apart genetic and environmental influences, are needed in the field [19, 22].

We sought to rigorously examine the associations between fetal growth and psychiatric and socioeconomic problems in a Swedish population cohort. Our outcomes included autism spectrum disorder (ASD), ADHD, psychotic or bipolar disorder, substance use problem, suicide

attempt, criminality, failing grades in grade 9, low educational attainment, and social welfare receipt. We estimated the magnitude of the associations from traditional, population-based epidemiological designs and examined the effect sizes using sibling-comparison models. Quasi-experimental approaches, such as sibling-comparison approaches, utilize design features to test alternative explanations [23]. By accounting for genetic and environmental factors that make siblings similar, sibling-comparisons offer a way to pull apart genetic and environmental confounding [23, 24]. Sensitivity analyses were used to test alternative explanations and address limitations inherent in the sibling-comparison approach [25].

Methods

Sample

After approval from the Institutional Review Boards at Karolinska Institutet and Indiana University, we created a prospective national cohort by linking information in the following Swedish registries: (1) the Medical Birth Register includes data on more than 99% of all pregnancies in Sweden; (2) the Multi-Generation Register contains information about the biological relationships for all individuals living in Sweden; (3) the Migration Register contains information on dates of migration in or out of Sweden; (4) the Cause of Death Register supplies dates and causes of all deaths; (5) the Patient Register contains diagnoses for all inpatient hospital admissions since 1973 and outpatient care since 2001; (6) the National Crime Register includes information about all criminal convictions; (7) the National School Register includes all subject grades at the end of grade nine since 1983; (8) the Education Register contains information on the highest level of completed formal education; and (9) the longitudinal integration database for health insurance and social studies (LISA) contains yearly assessments

of childbearing, marital, and social welfare status for all individuals at least 15 years old since 1990. Detailed information about these registers is available elsewhere [26].

The dataset began with 3,619,712 offspring born from 1973 to 2008. We removed multiple births (86,273, 2.4%) because birth outcomes are different in multiples as compared with singleton births [27]. We also removed offspring with missing birth weight information (9,888, 0.3%) as well as recorded gestational age values of less than 23 weeks or greater than 42 weeks and 6 days (49,374, 1.4%). Offspring with no sex information (3, <0.1%), invalid parity information (20, <0.1%), and those who had emigrated within the 25 year period (182,223, 5.0%) were removed. We also excluded offspring missing maternal identification numbers (158, <0.1%). The final sample consisted of 3,291,773 offspring born to 1,735,250 distinct biological mothers, representing 90.9% of all recorded Swedish births within the year range investigated.

ASD and ADHD were identified using inpatient and outpatient assessment information [28] from individuals born between 1980 and 2001 (N=2,032,803). In addition, we used a 2 year age criterion for ASD and ADHD diagnosis. For criminality, we used an age criterion of 15 years because of the Swedish legal age of responsibility. Therefore, the criminality sub-sample spanned the years 1973-1994 and included 2,044,992 individuals. For all other outcomes, we used a 12 year age criterion. Therefore, this sub-sample included 2,133,504 offspring born between 1973 and 1997.

Measures

Birth weight

To assess fetal growth, we utilized two different representations of birth weight while controlling for gestational age at birth. For the ordinal representation, birth weight was grouped into the following ranges: ≤ 2500 g, 2501-3000 g, 3001-3500 g, 3501-4000 g (referent), and ≥

4001 g. Continuously measured birth weight was converted to a linear scale centered at 3750 g (reference 0 point), the approximate mean of the sample.

Offspring outcomes

We predicted six indices of psychiatric problems previously shown to be reliable measures [28-32]. In particular, (1) *ASD* and (2) *ADHD* were indexed using validated [28, 33] inpatient and outpatient diagnoses according to International Classification of Disease (ICD)-9 and -10 for offspring born between 1980 and 2001 and being at least 2 years old at the time of diagnosis. As the ICD follows a strict definition of ADHD and ASD, results apply to the most severe cases of these disorders. In addition, it was not possible to classify ADHD cases according to subtype (i.e., combined, primarily hyperactive-impulsive and primarily inattentive type), since these were not recorded across the registers using the ICD. Offspring had to have been at least 12 years old to receive any of the following disorders: (3) *psychotic or bipolar disorder* was defined as first inpatient hospitalization for schizophrenia, bipolar disorder, or another non-organic psychotic disorder according to ICD-8, -9, and -10 criteria [29]; (4) *substance use problem* was defined as first inpatient hospitalization for a primary or secondary diagnosis of alcohol or any other non-nicotine substance use disorder [30]; (5) age at *suicide attempt* was gathered using inpatient hospitalization for a primary or secondary diagnosis [31]; and (6) *criminality* was indicated by the first occurrence of any criminal conviction from age 15 years, the age of legal responsibility in Sweden [32]. We chose not to examine broadly defined affective disorder because inpatient hospitalization for that diagnosis may indicate the presence of co-occurring suicidality or psychosis, and we had access to validated indicators of these associated possible outcomes [29, 31]. Respective ICD codes are presented in the Appendix

Table 1A, and it should be noted that clinical evaluations, not structured interviews, were used by diagnosing medical providers to determine primary diagnoses.

We predicted three indices of socioeconomic outcomes: (1) *failing grades* indexed poor school performance in grade 9 commensurate with a mean failing grade across 16 academic subjects [34]; (2) *education under 10 years* was an indication of low educational attainment [35] and (3) *social welfare receipt*, which was defined as the age of first receipt of government social welfare subsidies. For verification and converging support of these outcomes, we also predicted *low income* and *higher education* (further explained in the Appendix Figure 2A).

Covariates

The Medical Birth Register provided offspring sex, birth order, year of birth, and gestational age at birth. Measured maternal and paternal covariates included age at the offspring's birth, highest level of completed education by 2008 (to capture some socioeconomic variability across families), and lifetime history of any criminal conviction. All covariates were associated with both birth weight and the outcomes.

Analyses

We used Cox survival analysis for right-censored outcomes because not all offspring have lived through the study period. If offspring did not receive a diagnosis within the study period, they contributed person-time at risk until death, emigration, or the end date of follow-up (December 31, 2009), whichever came first. We used logistic regression analyses when predicting failing grades and education under 10 years because they were dichotomous outcomes. Thus, results are presented as hazard ratios (HR) or odds ratios (OR).

We fit a series of models for each outcome. All models controlled for offspring sex, birth order, and measures of linear and quadratic gestational age. Logistic models also controlled for

offspring year of birth. Because we always adjusted gestational age at birth, our predictor may be considered an index of fetal growth. The first statistical model used the ordinal representation of birth weight to estimate clinically-interpretable estimates of risk across outcomes. Second, we used a continuous representation of birth weight in two baseline models. One baseline model included both a linear and quadratic representation of birth weight, while the other baseline model only included the linear representation of birth weight. Akaike information criterion, a measure of relative merit that penalizes for model complexity, was used to select the best fitting model, either linear or quadratic. Third, we included offspring-specific (sex, birth order, linear and quadratic gestational age, and maternal and paternal age at childbearing) and parental-specific covariates (maternal and paternal highest level of education and history of criminal conviction) in an adjusted model of either continuous linear or quadratic representation of birth weight. Fourth, we fit a fixed effects model that clustered at the maternal level which accounted for factors that siblings share, including all genetic and environmental factors that make siblings similar [24]. Covariates that may vary between siblings (i.e., offspring sex, birth order, gestational age, and offspring year of birth [in logistic models]) were included in fixed effects models. Siblings were identified as individuals sharing a biological mother (e.g., full or maternal half-siblings).

Sensitivity analyses

We ran several sensitivity analyses to test for biases due to preterm births, examine whether there was converging evidence across related socioeconomic outcomes, and check assumptions inherent in the sibling-comparison design.

Results

Table 1 presents cohort demographics by birth weight category. Table 2 presents the number of offspring across outcomes by birth weight category.

Psychiatric problems

Figure 1 presents results from the baseline ordinal model (dark bars) with 95% confidence intervals (CI). The corresponding results using the continuous measure of birth weight (the solid line in Figure 1) also illustrate how fetal growth was associated with later psychiatric problems. For ease of interpretation, ordinal results are discussed here and continuous results are presented graphically.

Figure 1, panels a, b, and c present the strong inverse association between birth weight and ASD ($HR_{\text{Birth weight (BW): } \leq 2500g}$=1.79, 95% CI=1.64-1.96), ADHD ($HR_{\text{BW: } \leq 2500g}$=1.54, 95% CI=1.44-1.65), and psychotic or bipolar disorder ($HR_{\text{BW: } \leq 2500g}$=1.19, 95% CI=1.09-1.29) respectively. The associations remained robust when adjusting for offspring- and parental-specific covariates (not shown; see Appendix Table 2A). Also in Figure 1, the findings from fixed effects modeling, which compared differentially exposed siblings (light bars with 95% CI and the dotted line), showed consistently elevated effect sizes for these outcomes. Fetal growth was associated with ASD ($HR_{\text{BW: } \leq 2500g}$=2.44, 95% CI=1.99-2.97), ADHD ($HR_{\text{BW: } \leq 2500g}$=1.65, 95% CI=1.40-1.93), and psychotic or bipolar disorder ($HR_{\text{BW: } \leq 2500g}$=1.24, 95% CI=1.02-1.51) independent of the measured covariates and the comparison of differentially exposed siblings, consistent with a causal inference.

A different pattern of results was found when predicting suicide attempt and substance use problem (Figure 1, panel d and e), however. As can be noted in the dark bars in Figure 1, population models suggested that lower birth weight increased the risk for suicide attempt

($HR_{BW: \leq 2500g}$=1.19, 95% CI=1.11-1.28) and substance use problem ($HR_{BW: \leq 2500g}$=1.27, 95% CI=1.20-1.34). After adjusting for measured covariates (not shown; see Online Supplement, Table 2) and in fixed effects models (Figure 1, light bars), the associations with suicide attempt ($HR_{BW: \leq 2500g}$=0.94, 95% CI=0.81-1.10) and substance use problem ($HR_{BW: \leq 2500g}$=0.93, 95% CI=0.83-1.04) were fully attenuated.

The pattern of association was distinct when predicting criminality (Figure 1, panel f). More specifically, while population models showed that lower birth weight increased the risk for criminality ($HR_{BW: \leq 2500g}$=1.15, 95% CI=1.12-1.18), the direction of association switched in fixed effects models. In the fixed effects models, lower birth weight was slightly protective against criminality ($HR_{BW: \leq 2500g}$=0.87, 95% CI=0.83-0.92).

As can be seen in Figure 1, all psychiatric outcomes except suicide attempt and substance use problem were better explained by a quadratic representation of birth weight (see Appendix Table 3A for Akaike information criterion for linear and quadratic models). Adjusted models are not presented here or in Figure 1 for ease of interpretation. Parameter estimates across all ordinal bins are presented in Appendix Table 4A.

Socioeconomic outcomes

Figure 2, panels a, b, and c present findings across ordinal and continuous birth weight representation for failing grades, education under 10 years, and social welfare receipt respectively. Population estimates suggested that lower birth weight was associated with increased risk for failing grades ($HR_{BW: \leq 2500g}$=1.66, 95% CI=1.62-1.71) and education under 10 years ($HR_{BW: \leq 2500g}$=1.46, 95% CI=1.42-1.49). These are presented in Figure 2 via dark bars (ordinal) and solid line (continuous). Fixed effects models showed attenuated, though consistent results for failing grades ($HR_{BW: \leq 2500g}$=1.07, 95% CI=1.01-1.13) and education under 10 years

($HR_{BW: \leq 2500g}$=1.18, 95% CI=1.12-1.24), as can be seen via the light bars (ordinal) and dotted line (continuous). Thus, the results lend support to fetal growth being in the causal path towards failing grades and education under 10 years. A different pattern emerged for social welfare receipt, however (Figure 2, panel c). Although the population estimate for social welfare receipt showed that lower birth weights are associated with increased social welfare receipt ($HR_{BW: \leq 2500g}$=1.52, 95% CI=1.49-1.55), the relation was completely attenuated in the fixed effects model ($HR_{BW: \leq 2500g}$=1.00, 95% CI=0.95-1.05).

Sensitivity analyses

First, to test if results were biased by premature births, we limited the sample to full term births only. Appendix Figure 1A shows that associations are comparable to those found in main analyses, thus premature births were not driving the associations found. Second, we predicted two additional outcomes related to our main socioeconomic outcomes, low income and higher education. From these analyses we obtained converging evidence about the robust association between fetal growth and decreased odds of educational attainment, as well as the fully attenuated relation between fetal growth and economic stability (Appendix Figure 2A). Third, we performed analyses to address some of the assumptions of the sibling-comparison design. To address concerns about the generalizability of findings from offspring with siblings to those without, we compared the population estimates in families with multiple children to those with only one child. Appendix Figure 3A shows that baseline population estimates were not different between offspring with one or more siblings as compared to only children. To address concerns about the generalizability of the findings from differentially exposed sibling to other populations, we conducted cousin-comparisons. Appendix Figure 4A presents the cousin-comparison results showing a commensurate pattern of results to the main analyses. These results suggest that

assumptions in sibling-comparison analyses (e.g., no carry-over effects) may not account for our conclusions.

Discussion

The current study examined the degree to which familial confounding, due to genetic and shared environmental factors, accounts for the associations between fetal growth, indicated by birth weight while controlling for gestational age, and psychiatric and socioeconomic problems. Across outcomes, and in agreement with most previous research [2-8, 26, 36], the population estimates suggested that impaired fetal growth, as evidenced by lower birth weights, was associated with greater risk of each outcome. Results from sibling-comparison analyses showed that associations are consistent with causal inferences in an outcome-dependent manner. After fitting sibling-comparison fixed effects models, the results support causal inferences between fetal growth and ASD, as well as ADHD. Despite some attenuation in fixed effects models, the relation between fetal growth and psychotic or bipolar disorder, as well as failing grades and education less than 10 years, also supports a causal inference. Therefore, genetic and/or environmental factors specific to fetal development, as indexed by lower birth weight, influence the likelihood of these outcomes. In contrast, our results showed attenuation of the associations between fetal growth and suicide attempt, substance use problem, and social welfare receipt, thus suggesting that these associations are primarily due to selection effects correlated with fetal growth. Additionally, sensitivity analyses provided evidence against alternative explanations for the findings.

Associations consistent with a causal inference

The associations between birth weight and ADHD and ASD were independent of shared familial confounds and statistical covariates, as the magnitudes of association remained significantly elevated in fixed effects models. Though some previous research has reported null findings [1, 5, 18], the current results build on previous co-twin control [2, 4, 10-12] and epidemiological study findings [3]. The associations between birth weight and psychotic or bipolar disorder were also independent of shared familial confounds and statistical covariates, although the magnitudes of association were attenuated in fixed effects models. Even more attenuated, though still present, were the associations between birth weight and educational attainment variables in the fixed effects models [5-8, 36]. The interpretation of sensitivity analyses that examined the associations in full term births only, in families with only one child, and when comparing differentially exposed cousins (see Appendix Figures 1A, 3A, and 4A respectively) did not differ from the main results. Therefore, overall, our findings lend greater support to the conclusion that fetal growth is along a causal pathway for these outcomes. Our findings also complement previous sibling-comparison research focusing on the long-term outcomes following early gestational age at birth [26].

Comparing the associations across these outcomes, fetal growth appears to be more strongly related to early-onset neurodevelopmental disorders such as ADHD and ASD than for distal markers of neurodevelopmental problems, such as educational problems and later-onset disorders, such as psychotic or bipolar disorder. As evidence across studies converge on a consistent picture of the role of fetal growth on these outcomes, future research must examine possible mediating mechanisms. For example, previous research has shown white matter abnormalities due to brain injury associated with low birth weight [37]. Other differences in

brain development that correspond with neurodevelopmental problems, such as the amount of cortical surface area, brain volume, and caudate volume, have also been noted even across variations within normal birth weight [38]. Poor in utero nutrition may also be contributing to different fetal growth and altered brain development [39]. ADHD and ASD have been shown to share common genetic etiology [40], which will also have to be explored.

Interestingly, we also found that impaired fetal growth was associated with a decreased likelihood of criminality after fixed effects modeling and across the sensitivity analyses. The direction of this association is in contrast to the increased likelihood of criminality for impaired fetal growth in our population-based model. Our fixed effects findings support previous fetal growth research [5] and extend associations found for early gestational age and criminality [26, 41]. Fetal growth impaired individuals may display personality characteristics linked with decreased risk-taking behaviors, receive increased parental monitoring, and/or form fewer relationships with delinquent peers. Future investigations into violent versus nonviolent crimes using advanced modeling may elucidate the association further [42].

Associations fully attenuated

Associations between fetal growth and substance use problem, suicide attempt, and social welfare receipt, presented a different pattern of associations. In particular, we found that once the genetic and environmental factors that siblings share were controlled, the relation between fetal growth and these outcomes was fully attenuated. We also found converging evidence for social welfare receipt when predicting low income (see Appendix Figure 2A). The lack of association with substance use problem is in contrast to a previous co-twin control [21] and an epidemiological [5] study showing heavier infants were at increased risk for alcohol and drug use than lower birth weight infants. More research is needed, however, as substance use outcomes

vary across studies. Our findings suggest that selection factors that make siblings similar and co-occur with variability in fetal growth account for these associations.

Strengths and limitations

We used a large, well-validated, population-based dataset. The size and scope of the dataset provided us the opportunity to examine rare and serious outcomes while studying the specificity of our findings across a broad range of outcomes. Further, the data structure allowed us to utilize quasi-experimental designs (e.g., sibling- and cousin-comparison) with precise measures of predictors and covariates. This is one of the first studies on fetal growth to have the power to examine associations using a sibling-comparison design, an important step toward supporting or refuting causal inferences. The sibling-comparison design can be considered in light of other advantages and limitations of other quasi-experimental approaches. Co-twin control studies, or the comparison of differentially exposed identical twins, have high internal validity because they can rule out genetic confounding. Genetic confounding may be important in these associations as studies have suggested that obstetric complications are more common among certain psychiatric outcomes (e.g. schizophrenia [43]). The co-twin control approach may have limited generalizability, however, because fetal growth differences in twins may be etiologically distinct from differences in birth weight among singletons, and twins have a greater risk for growth restriction in utero than singletons [27].

Through the sensitivity analyses of cousin-comparisons and comparing outcomes across offspring with and without siblings, we explicitly tested some assumptions of the sibling-comparison design [24]. We included a sensitivity test examining if associations were driven by gestational age extremes and searched for converging findings across related socioeconomic outcomes. For example, we showed that impaired fetal growth is associated with decreased

likelihood of achieving a higher education (see Appendix Figure 2A), similar to our findings predicting an increased likelihood of failing grades and education less than 10 years with impaired fetal growth. We also verified categorically measured birth weight findings with continuously measured birth weight and were thus able to increase statistical power while examining the full continuum of birth weight. Further, it should be noted that although our predictor was birth weight, we adjusted all associations for gestational age at birth. Therefore, we consider the predictor an index of fetal growth.

Despite these strengths, however, several limitations must be considered and addressed in future research. Sibling-comparisons are not randomized controlled studies; therefore, the design cannot rule out all possible confounding factors and causation cannot be proven. For example, offspring-specific genetic factors that influence birth weight could account for the associations [24, 25]. If genetic factors that influence fetal growth also influence the likelihood of outcomes, fetal growth indicators would not necessarily be in the causal pathway. Yet, similar results of independent risk associated with fetal growth factors have been shown by comparing birth weight discordant monozygotic twins [2], which suggest such genetic factors do not explain the associations. Fixed effects models also have lower statistical power than population-based estimates (44), but we sought to address this limitation by utilizing continuously measured birth weight. Additional quasi-experimental research that relies on methods with different assumptions and limitations than the sibling-comparison approach is warranted [23]. Replication in other countries, especially in countries differing in health care availability, also is needed.

Implications

The current sibling-comparison study examined the long-term psychiatric and socioeconomic implications of low birth weight adjusted for gestational age. Our findings

contribute to the etiological theory of neurodevelopmental disorders and socioeconomic outcomes, as causal inferences were divided by outcome type. Specifically, the results suggest that efforts be made to reduce the incidence of low birth weight births, as associations predicting neurodevelopmental outcomes were consistent with a causal interpretation (i.e., ASD, ADHD, psychotic or bipolar disorder, failing grades, and education less than 10 years). Results also suggest that public health initiatives provide services that target risks co-occurring with impaired fetal growth, as the associations between birth weight and substance use problem, suicide attempt, and social welfare receipt were due to selection factors that co-occur with birth weight. Our findings also open an interesting line for future researchers to explore what factors associated with impaired fetal growth contribute to the decreased risk of criminality we identified in sibling comparison analyses. Overall, the current study emphasizes the importance of continued research on the role of fetal growth factors in offspring psychiatric and socioeconomic problems.

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Table 1. Demographic characteristics of 3,291,773 offspring born 1973-2008 in Sweden by birth weight.

Covariates	Birth year	Statistic	Birth weight category (g) ≤ 2,500 (*n* = 114,580)		2,501-3,000 (*n* = 366,500)		3,001-3,500 (*n* = 1,075,447)		3,501-4,000 (*n* = 1,152,337)		≥ 4,000 (*n* = 583,909)	
Offspring (*n* = 3,921,773)	1973-2008											
Female		(n, %[a])	58,657	51.19	207,481	56.61	573,332	53.31	533,202	46.27	220,119	37.76
Gestational age (days)		(M, SD)	245.46	25.53	271.19	12.10	278.14	9.41	282.14	8.27	285.24	7.77
Maternal (*n* = 1,732,107)	1924-1995											
Age at birth (yrs)		(M, SD)	28.85	5.67	28.43	5.36	28.59	5.19	28.96	5.10	29.55	5.06
Nationality (Swedish)		(n, %)	54,045	83.77	169,706	83.00	491,255	84.77	518,302	87.12	254,761	88.68
Upper secondary education (min 3 yrs)		(n, %)	31,870	49.35	105,639	51.62	323,120	55.71	347,214	58.32	170,492	59.31
Adult severe psychopathology		(n, %)	1,748	2.71	4,493	2.20	10,606	1.83	9,629	1.62	4,377	1.52
Criminality		(n, %)	8,939	13.84	26,443	12.92	65,981	11.38	61,356	10.31	28,207	9.81
Paternal (*n* = 1,725,359)	1904-1993											
Age at birth (yrs)		(M, SD)	31.75	6.55	31.38	6.28	31.49	6.07	31.78	5.96	32.28	5.91
Nationality (Swedish)		(n, %)	52,049	83.61	165,781	82.69	485,000	84.50	518,434	87.04	259,048	89.02
Upper secondary education (min 3 yrs)		(n, %)	27,192	43.63	90,199	44.92	274,812	47.82	294,778	49.44	145,192	49.84
Adult severe psychopathology		(n, %)	1,345	2.16	4,033	2.01	10,059	1.75	9,399	1.58	4,172	1.43
Criminality		(n, %)	25,953	41.64	81,223	40.45	219,628	38.22	216,353	36.28	101,834	34.96

Notes: [a] percentage of individuals by birth weight group, for offspring, the total number by birth weight group is listed in the column header, for mother and father variables, the total number of distinct mothers and fathers are listed in the left column and percentages are based on the number of non-missing cases for each variable, M = mean, SD = standard deviation

Table 2. Psychiatric and socioeconomic outcomes by birth weight.

Outcomes	Birth year	Total number of persons	Birth weight category (g)									
			≤ 2,500 (n = 114,580)		2,501-3,000 (n = 366,500)		3,001-3,500 (n = 1,075,447)		3,501-4,000 (n = 1,152,337)		≥ 4,000 (n = 583,909)	
			n	KME	n	KME	n	KME	n	KME	n	KME
Psychiatric Morbidity												
ADHD[a]	1980-2001	2,032,803	521	0.75	925	0.43	2,125	0.33	2,279	0.33	1,437	0.41
ASD[a]	1980-2001	2,032,803	303	0.43	594	0.27	1,346	0.21	1,497	0.21	953	0.27
Psychotic or Bipolar[b]	1973-1997	2,308,032	631	1.34	1,724	1.05	4,293	0.94	4,153	0.89	1,881	0.87
Suicide Attempt[b]	1973-1997	2,308,032	1,094	2.19	3,728	2.11	9,138	1.84	8,272	1.62	3,567	1.51
Substance Use Problem[b]	1973-1997	2,308,032	1,584	2.70	5,130	2.68	13,347	2.48	13,691	2.28	5,698	2.20
Criminality[b]	1973-1994	2,044,992	8,810	15.64	31,178	15.77	87,032	15.59	91,071	15.88	44,133	16.48
Socioeconomic Outcomes												
Failing Grades[b]	1973-1992	1,776,454	11,635	17.13	35,962	16.52	89,712	14.63	72,391	11.42	22,626	7.57
Education Under 10 yrs[b]	1973-1991	1,689,102	18,502	32.79	60,246	30.09	163,611	28.80	165,487	28.23	79,515	28.98
Social Welfare Reciept[b]	1973-1990	1,609,646	15,535	32.55	51,803	30.58	128,141	27.12	119,124	24.74	54,714	23.69

Notes: ADHD=Attention Deficit Hyperactivity Disorder, ASD=Autism Spectrum Disorder, KME=Kaplan Meier survival estimate,
[a]KME at 25 years old, [b]KME at 35 years old

Figure Legend.

Figure 1. Associations derived from continuous (line) and ordinal (bar with 95% CI) representation of birth weight when predicting psychiatric outcomes: (a) ADHD, (b) ASD, (c) psychotic or bipolar disorder, (d) suicide attempt, (e) substance use problem, and (f) criminality. Baseline, population-wide estimates are shown via the solid line and dark bars. Sibling-comparison, fixed effects models are shown via dotted lines and light bars. Reference group are those born in the 3,500 – 4,000 g birth weight category. The maintenance of association magnitude across population and sibling-comparison models, consistent with a causal inference, can be noted when predicting ADHD, ASD, and psychotic or bipolar disorder only. A protective effect can be noted when predicting criminality in the decrease of association in the sibling-comparison model.

Figure 2. Associations derived from continuous (line) and ordinal (bar with 95% CI) representation of birth weight when predicting socioeconomic outcomes: (a) failing grades, (b) education under 10 years, and (c) social welfare receipt. Baseline, population-wide estimates are shown via the solid line and dark bars. Sibling-comparison, fixed effects models are shown via dotted lines and light bars. Reference group are those born in the 3,500 – 4,000 g birth weight category. Though attenuated, the maintenance of association magnitude across population and sibling-comparison models, consistent with a causal inference, can be noted when predicting failing grades and education under 10 years only.

Figure 1.

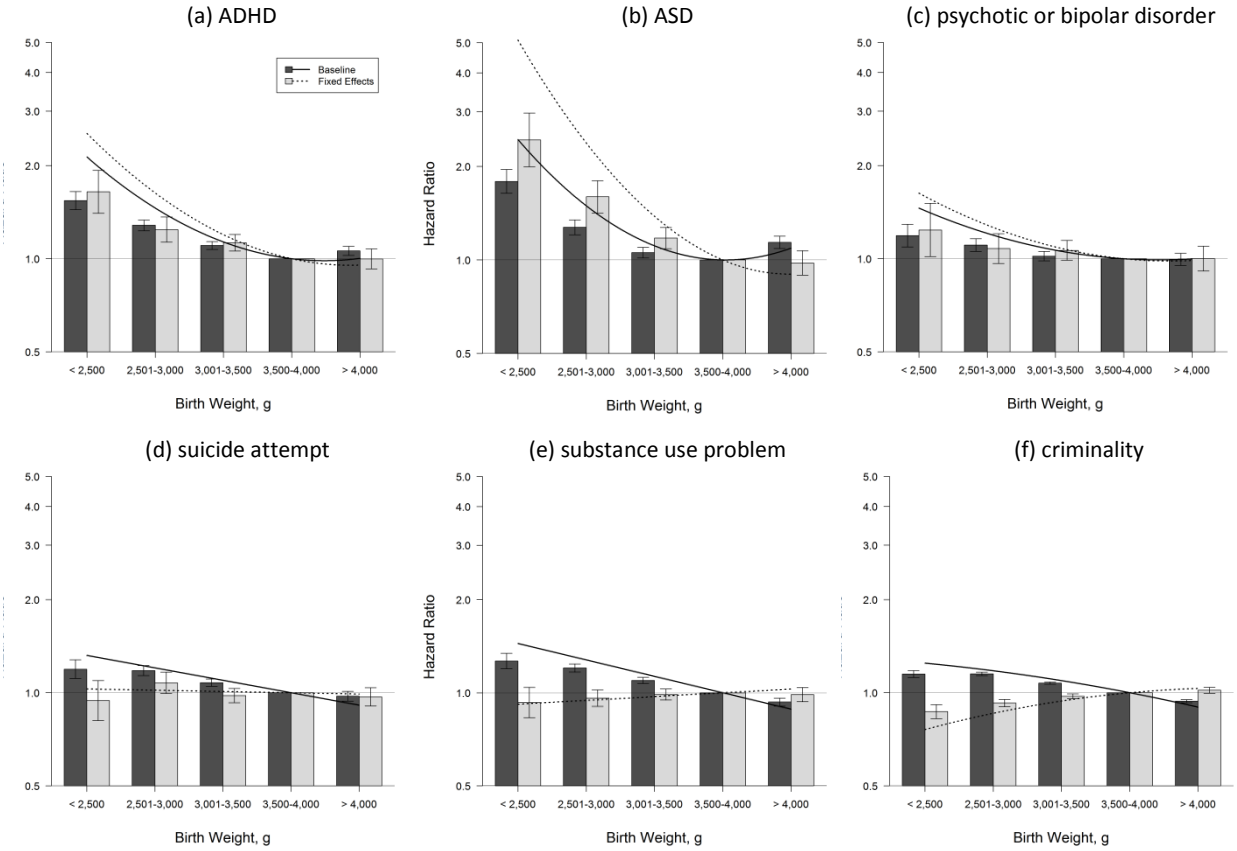
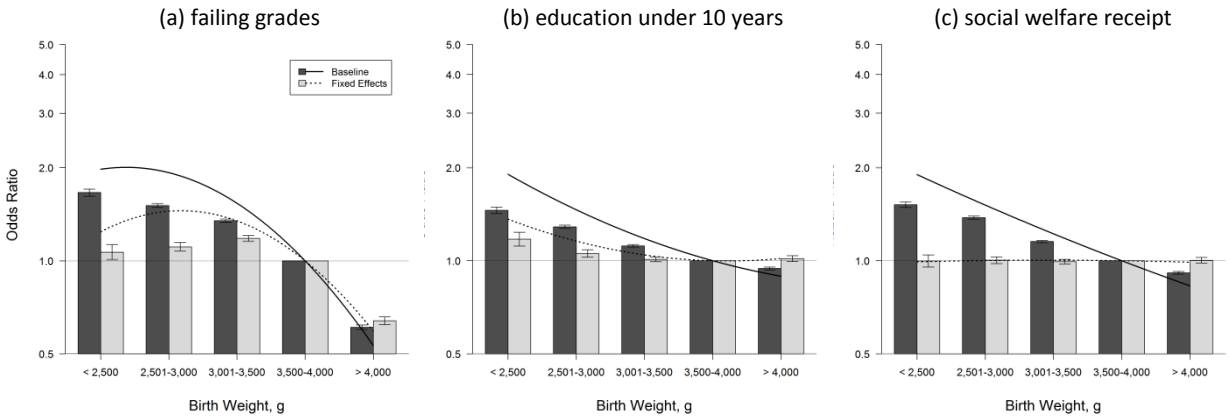

(a) ADHD
(b) ASD
(c) psychotic or bipolar disorder
(d) suicide attempt
(e) substance use problem
(f) criminality
Baseline
Fixed Effects
Hazard Ratio
5.0
4.0
3.0
2.0
1.0
0.5
< 2,500
2,501-3,000
3,001-3,500
3,500-4,000
> 4,000
Birth Weight, g

Figure 2.


(a) failing grades
(b) education under 10 years
(c) social welfare receipt
Baseline
Fixed Effects
Odds Ratio
5.0
4.0
3.0
2.0
1.0
0.5
< 2,500
2,501-3,000
3,001-3,500
3,500-4,000
> 4,000
Birth Weight, g

Appendix: Fetal growth and psychiatric and socioeconomic problems: A population-based sibling-comparison

Table 1A. International Classification of Disease (ICD) code used to classify outcomes with outcome description.

Outcome	Data Source	ICD Version	ICD Codes	Description
Psychiatric Problems				
ADHD	PR	9,10	314, F90	Hyperkinetic syndrome and attention-deficit hyperactivity disorders
ASD	PR	9, 10	299, F84	Includes disintegrative psychosis, Heller's syndrome, and schizophrenic syndrome of childhood
Psychotic or Bipolar Disorder	PR	8, 9, 10	295, F20 296.1, 296.3, 296A-296E, 296W, F30-F31 291, 292, 296.0, 296.2, 296.9, 297-299, 296B, 296X, F32.3 x.5 in F10-F19	Schizophrenia Bipolar disorder Other non-organic psychoses
Suicide Attempt	PR	8, 9, 10	E950-E959, E980-E989, X60-X84, Y870, Y10-Y34, Y872	Certain and uncertain attempts including violent, non-violent, other
Substance Use Problem	PR	8, 9, 10	303, 304, 305A, 305X, F10 (except x.5), F11-F19 (except x.5)	Alcohol and drug abuse (excludes nicotine)
Criminality	NCR	NA	NA	Earliest conviction date for any criminal act
Socioeconomic Outcomes				
Failing Grades	NSR	NA	NA	Poor school performance across all 16 academic subjects in grade 9 (about age 16)
Education under 10 years	ER	NA	NA	Low educational attainment
Higher Education	ER	NA	NA	Three or more years of postsecondary education
Social Welfare Benefits	LISA	NA	NA	Age at first receipt of government social welfare subsidies

Note: ASD = Autism spectrum disorder; PR = Patient Register; NCR = National Crime Register; NSR = National School Register; ER = Education register; MBR = Medical Birth Register

Table 2A. Unstandardized linear and quadratic regression coefficients for the baseline, adjusted, and fixed effects models.

	Baseline Model				**Adjusted Model**				**Fixed Effects Model**			
	Linear term		Quadratic term		Linear term		Quadratic term		Linear term		Quadratic term	
Outcomes	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE
Psychiatric Problems												
ASD	-0.003	0.005	**0.011**	**0.001**	0.004	0.005	**0.010**	**0.001**	**-0.072**	**0.011**	**0.012**	**0.002**
ADHD	**-0.020**	**0.003**	**0.007**	**0.001**	-0.004	0.003	**0.007**	**0.001**	**-0.038**	**0.009**	**0.007**	**0.002**
Psychotic or Bipolar Disorder	**-0.011**	**0.004**	**0.003**	**0.001**	-0.001	0.004	**0.003**	**0.001**	-0.017	0.012	0.004	0.002
Suicide Attempt	**-0.031**	**0.003**	-	-	**-0.012**	**0.003**	-	-	-0.003	0.008	-	-
Substance Use Problem	**-0.041**	**0.003**	-	-	**-0.022**	**0.003**	-	-	0.009	0.006	-	-
Criminality	**-0.033**	**0.001**	**-0.001**	**0.000**	**-0.014**	**0.001**	**-0.001**	**0.000**	**0.016**	**0.003**	**-0.002**	**0.001**
Socioeconomic Outcomes												
Failing Grades	**-0.177**	**0.002**	**-0.011**	**0.000**	**-0.153**	**0.002**	**-0.011**	**0.000**	**-0.137**	**0.004**	**-0.013**	**0.001**
Education Under 10 yrs	**-0.047**	**0.001**	**0.003**	**0.000**	**-0.031**	**0.001**	**0.003**	**0.000**	-0.004	0.003	**0.003**	**0.001**
Social Welfare Receipt	**-0.065**	**0.001**	**0.001**	**0.000**	**-0.038**	**0.001**	**0.001**	**0.000**	-0.003	0.003	0.000	0.000

Note: ADHD=Attention Deficit Hyperactivity Disorder; ASD=Autism Spectrum Disorder; b=maximum likelihood estimate of the unstandardized regression coefficient; SE = estimated standard error; A dash(-) indicates that the p-value of the Wald chi-square test statistic for the quadratic parameter is greater than 0.05, and therefore not included in the model; bold coefficients have p-value < 0.05.

Table 3A. Comparison of Akaike information criterion fit indices across baseline linear and quadratic candidate models.

The model selection Table A3 compares the Akaike information criterion (AIC) for the baseline model with linear (L) birth weight only and the baseline model with both linear and quadratic (L+Q) birth weight. The column labeled "AIC-min" indicates which of the two candidate models (L or L+Q) yielded the lowest AIC. The observed difference, $\Delta AIC = AIC_L - AIC_{L+Q}$, provides a measure of relative merit that is free of scaling constants and can be interpreted as strength of evidence for model selection purposes [44].

Table 3A. Comparison of AIC values for linear and quadratic candidate models.

	Candidate Model			
Outcome	Linear BW	with Quadratic BW	AIC-min	ΔAIC
Psychiatric Problems				
ADHD	844471.23	844370.62	L + Q	100.61
ASD	452237.10	452102.20	L + Q	134.90
Psychotic or Bipolar Disorder	539246.73	539235.29	L + Q	11.44
Suicide Attempt	863605.97	863607.04	L	-1.07
Substance Use Problem	1303851.20	1303852.90	L	-1.70
Criminality	7995423.10	7995413.10	L + Q	10.00
Socioeconomic Outcomes				
Failing Grades	1347757.50	1346626.00	L + Q	1131.50
Education under 10 yrs	1839981.20	1839871.00	L + Q	110.20
Social Welfare Receipt	10651879.00	10651870.00	L + Q	9.00

Note: BW = birth weight; ADHD = Attention Deficit Hyperactivity Disorder; ASD = Autism Spectrum Disorder; L = model with linear birth weight only; L+Q = baseline model with both linear and quadratic birth weight

Table 4A. Odds or Cox hazard regression parameter estimates for baseline and fixed effects models using ordinal birth weight.

Table 4A presents the unstandardized regression coefficients with standard errors and the point estimates, either Odds Ratios or Hazard Ratios, with 95% confidence intervals associated with the ordinal bins of birth weight across baseline and fixed effects models. The baseline estimates presented here correspond with the point estimates presented in Figure 1 within the main paper.

Estimates for fixed effects models using ordinal representation of birth weight provide a sensitivity analysis to examine the sibling comparison results absent of assumptions about the underlying pattern (i.e., linear or quadratic) of the associations between birth weight and the indices of mortality and morbidity. Figures 1 and 2 in the main paper provide a graphical comparison of the baseline and fixed effects models using ordinally represented birth weight. The fixed effects results using ordinal representation of birth weight give commensurate results with analyses based on linear and quadratic modeling presented in the main analyses. It can be noted, however, that the confidence intervals around fixed effects estimates using ordinal bins are larger than those presented in the main analyses due to the reduced statistical power in moving from a continuous representation of birth weight to ordinal bins. These results suggest that assumptions about the shape of model fitting using families with multiple offspring (which are the only informative families for the sibling comparison estimates) do not account for the fixed effects results using the continuous index of birth weight.

Table 4A.

Outcome	Model	BW bin (gm)	Maximum Likelihood Parameters					
			b	SE	Pr > ChiSq	HR/OR	95%LCL	95%UCL
Psychiatric Problems								
ADHD	**Baseline**	**≤ 2500**	0.433	0.03	<.0001	1.542	1.442	1.649
		2501-3000	0.249	0.02	<.0001	1.283	1.232	1.335
		3001-3500	0.099	0.01	<.0001	1.104	1.072	1.136
		≥ 4001	0.059	0.02	0.001	1.061	1.025	1.097
	Fixed effects	**≤ 2500**	0.498	0.08	<.0001	1.646	1.403	1.932
		2501-3000	0.217	0.05	<.0001	1.243	1.131	1.365
		3001-3500	0.120	0.03	0.000	1.127	1.059	1.199
		≥ 4001	-0.001	0.04	0.971	0.999	0.927	1.076
ASD	**Baseline**	**≤ 2500**	0.582	0.04	<.0001	1.790	1.639	1.955
		2501-3000	0.242	0.03	<.0001	1.274	1.206	1.346
		3001-3500	0.055	0.02	0.007	1.056	1.015	1.099
		≥ 4001	0.131	0.02	<.0001	1.140	1.089	1.193
	Fixed effects	**≤ 2500**	0.890	0.10	<.0001	2.435	1.994	2.973
		2501-3000	0.469	0.06	<.0001	1.598	1.418	1.801
		3001-3500	0.162	0.04	<.0001	1.176	1.087	1.273
		≥ 4001	-0.022	0.05	0.636	0.978	0.893	1.072
Psychotic or Bipolar Disorder	**Baseline**	**≤ 2500**	0.172	0.04	<.0001	1.188	1.092	1.293
		2501-3000	0.102	0.02	<.0001	1.108	1.056	1.162
		3001-3500	0.020	0.02	0.271	1.020	0.985	1.056
		≥ 4001	-0.004	0.02	0.849	0.996	0.952	1.041
	Fixed effects	**≤ 2500**	0.214	0.10	0.035	1.239	1.016	1.511
		2501-3000	0.076	0.06	0.177	1.079	0.966	1.206
		3001-3500	0.062	0.04	0.097	1.064	0.989	1.146
		≥ 4001	0.002	0.05	0.970	1.002	0.913	1.099
Suicide Attempt	**Baseline**	**≤ 2500**	0.176	0.04	<.0001	1.192	1.112	1.279
		2501-3000	0.166	0.02	<.0001	1.180	1.137	1.225
		3001-3500	0.075	0.01	<.0001	1.078	1.049	1.108
		≥ 4001	-0.025	0.02	0.174	0.975	0.940	1.011
	Fixed effects	**≤ 2500**	-0.058	0.08	0.447	0.944	0.813	1.095
		2501-3000	0.074	0.04	0.068	1.077	0.995	1.166
		3001-3500	-0.021	0.03	0.447	0.980	0.929	1.033
		≥ 4001	-0.030	0.03	0.386	0.970	0.906	1.039
Substance Use Problem	**Baseline**	**≤ 2500**	0.237	0.03	<.0001	1.267	1.196	1.342
		2501-3000	0.185	0.02	<.0001	1.203	1.166	1.241
		3001-3500	0.092	0.01	<.0001	1.097	1.072	1.122
		≥ 4001	-0.068	0.01	<.0001	0.934	0.907	0.961

Table 4A cont.

Outcome	Model	BW bin (gm)	Maximum Likelihood Parameters					
			b	SE	Pr > ChiSq	HR/OR	95%LCL	95%UCL
Substance Use Problem	**Fixed effects**	**≤ 2500**	-0.072	0.06	0.210	0.930	0.831	1.041
		2501-3000	-0.039	0.03	0.215	0.962	0.904	1.023
		3001-3500	-0.012	0.02	0.573	0.988	0.948	1.030
		≥ 4001	-0.013	0.03	0.620	0.987	0.936	1.040
Criminality	**Baseline**	**≤ 2500**	0.139	0.01	<.0001	1.149	1.120	1.179
		2501-3000	0.141	0.01	<.0001	1.151	1.136	1.167
		3001-3500	0.072	0.00	<.0001	1.075	1.065	1.084
		≥ 4001	-0.063	0.01	<.0001	0.939	0.929	0.950
	Fixed effects	**≤ 2500**	-0.140	0.03	<.0001	0.869	0.825	0.915
		2501-3000	-0.077	0.01	<.0001	0.926	0.901	0.952
		3001-3500	-0.026	0.01	0.004	0.974	0.957	0.992
		≥ 4001	0.019	0.01	0.096	1.019	0.997	1.041
Socioeconomic Outcomes								
Failing Grades	**Baseline**	**≤ 2500**	0.509	0.01	<.0001	1.664	1.620	1.708
		2501-3000	0.412	0.01	<.0001	1.509	1.487	1.532
		3001-3500	0.299	0.01	<.0001	1.348	1.333	1.363
		≥ 4001	-0.495	0.01	<.0001	0.610	0.600	0.620
	Fixed effects	**≤ 2500**	0.065	0.03	0.023	1.067	1.009	1.128
		2501-3000	0.104	0.02	<.0001	1.110	1.076	1.145
		3001-3500	0.167	0.01	<.0001	1.182	1.157	1.207
		≥ 4001	-0.446	0.01	<.0001	0.640	0.622	0.659
Education under 10 yrs	**Baseline**	**≤ 2500**	0.376	0.01	<.0001	1.456	1.421	1.492
		2501-3000	0.253	0.01	<.0001	1.288	1.272	1.305
		3001-3500	0.112	0.00	<.0001	1.118	1.108	1.128
		≥ 4001	-0.057	0.01	<.0001	0.945	0.934	0.955
	Fixed effects	**≤ 2500**	0.161	0.03	<.0001	1.175	1.116	1.237
		2501-3000	0.054	0.01	0.000	1.055	1.027	1.085
		3001-3500	0.011	0.01	0.221	1.011	0.993	1.029
		≥ 4001	0.017	0.01	0.124	1.017	0.995	1.039
Social Welfare Receipt	**Baseline**	**≤ 2500**	0.417	0.01	<.0001	1.518	1.488	1.548
		2501-3000	0.321	0.01	<.0001	1.379	1.364	1.394
		3001-3500	0.143	0.00	<.0001	1.154	1.145	1.163
		≥ 4001	-0.090	0.01	<.0001	0.914	0.905	0.924
	Fixed effects	**≤ 2500**	-0.001	0.02	0.956	0.999	0.954	1.045
		2501-3000	0.005	0.01	0.724	1.005	0.980	1.030
		3001-3500	-0.007	0.01	0.420	0.993	0.977	1.010
		≥ 4001	0.004	0.01	0.710	1.004	0.983	1.026

Figure 1A. Fixed effects parameter estimates when limiting sample to full term births only.

Compared with parameter estimates from the main analyses, which included all gestational ages, results from analyses limited to full term births did not substantially alter the results (Figure 1A). This suggests that associations presented in main analyses were not biased by extremely premature or late births. Figure 1A presents main analyses figures as well as those limited to full term births only (right column). As can be seen in Figure 1A, when restricted to full term births only (right figure), parameters corresponding to the smallest ordinal category of birth weight were attenuated as compared with main analyses (left figure). Small sample size may also contribute to this attenuation.

Figure 1A. Comparison of birth weight predicting psychiatric and socioeconomic outcomes across all gestational ages (left column) and full term only (right column) births.

Psychiatric Problems

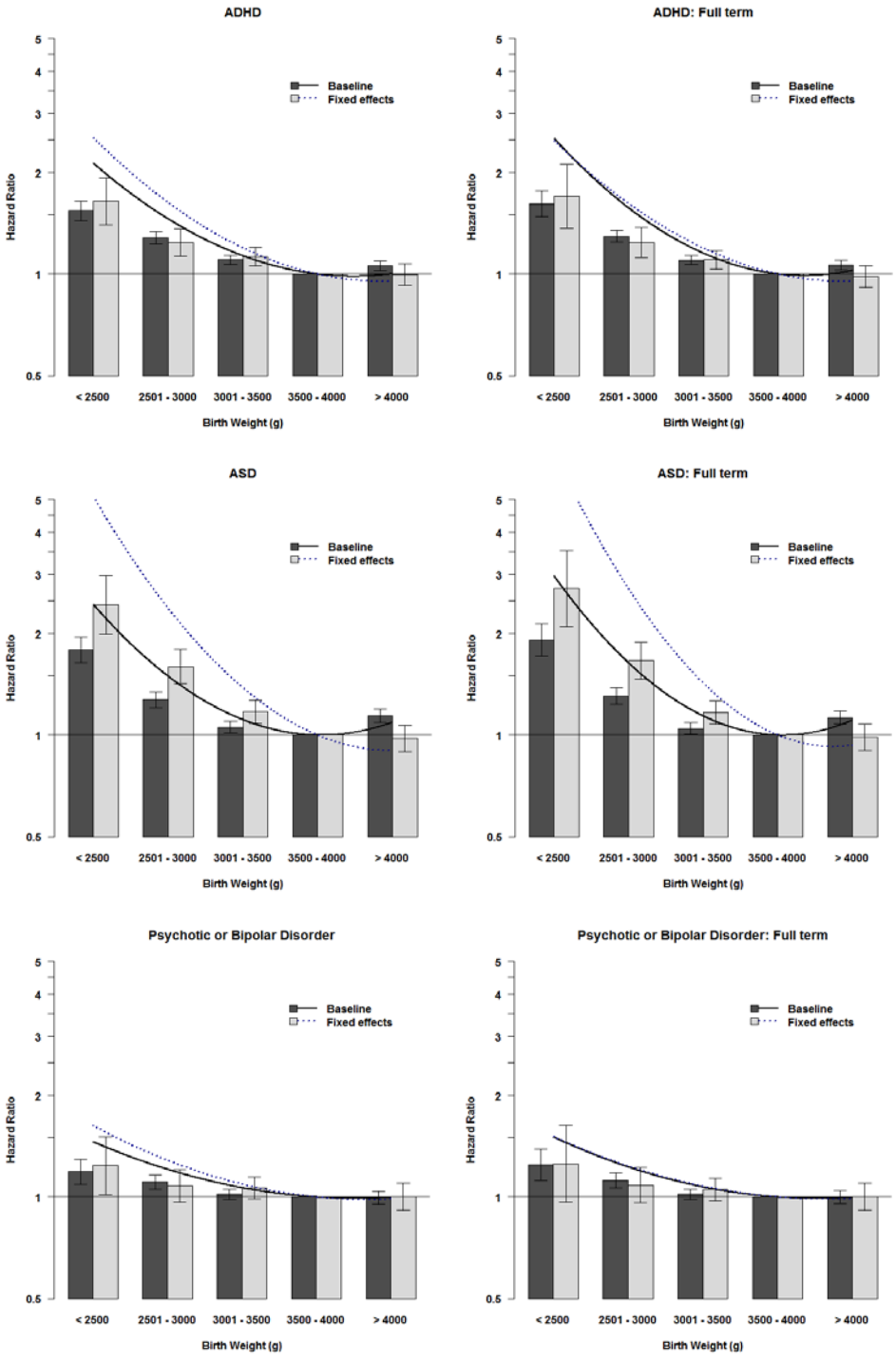


Figure 1A cont.

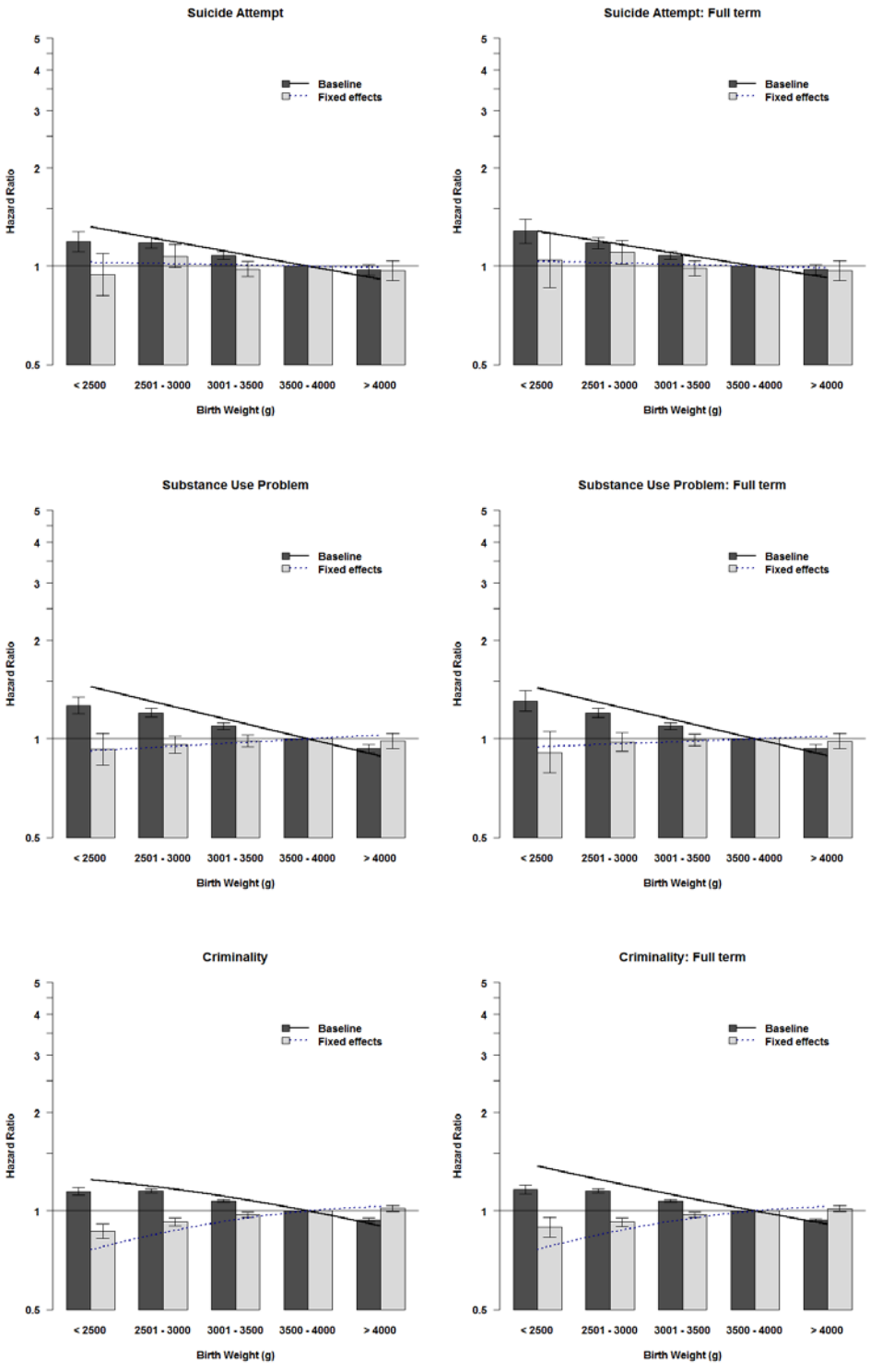


Figure 1A cont.

Socioeconomic Outcomes

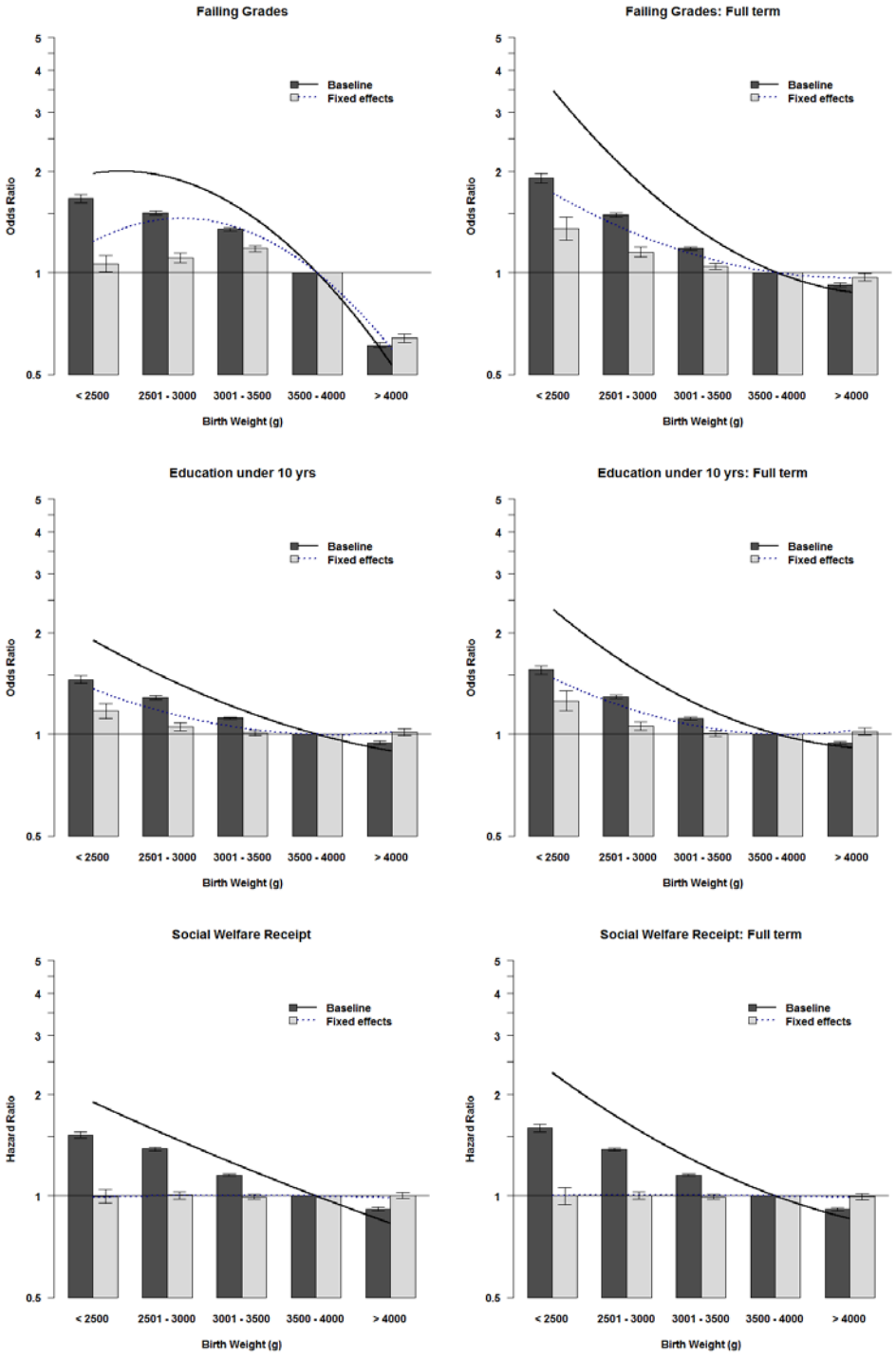


Figure 2A. Continuous and ordinal baseline and fixed effects figures predicting low income and higher education.

We predicted two additional socioeconomic outcomes to examine if we could provide converging evidence with the outcomes predicted in the main analyses. We predicted *low income*, from the LISA database, defined as being in the lowest 20th percentile income bracket for 2 consecutive years. *Higher education* was defined as three or more years of postsecondary education and was gathered from the Education Register. Only offspring born 1973-1983, whose age made it possible to achieve this level of education, were included in this sample.

As can be seen in Figure 2A, below, the baseline and fixed effects findings for these outcomes support those presented in the main analyses; lower birth weight is associated with increased odds of *Low Income* only in baseline analyses. Similar to *Social Welfare Receipt*, the relation was fully attenuated following fixed effects modeling. Low birth weight was also found to decrease the odds of achieving a *Higher Education*, and similar to *Failing Grades* and *Education Under 10 years*, this association was consistent in the fixed effects model.

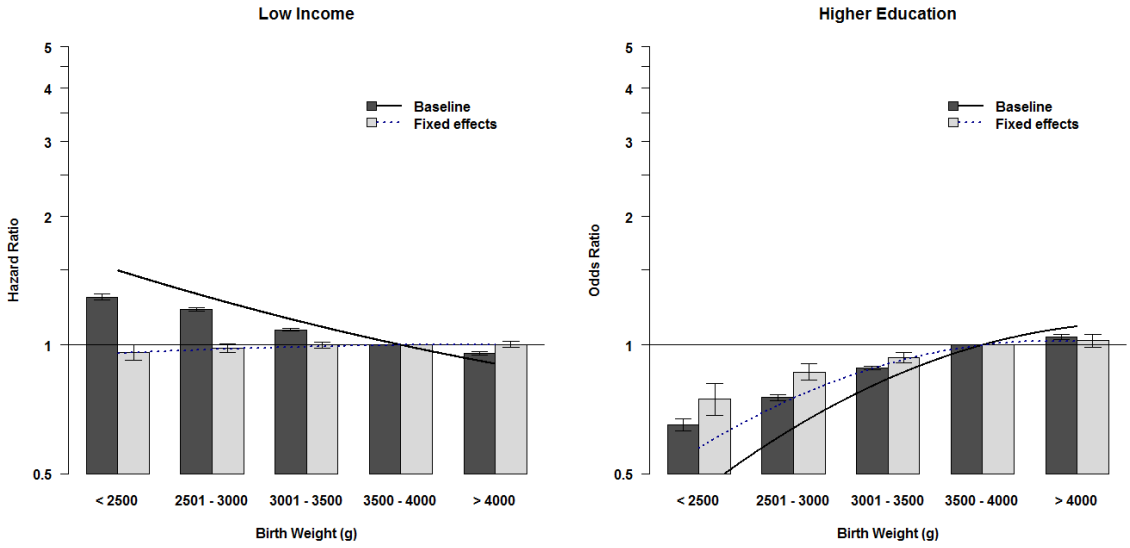


Figure 3A. Comparison of baseline parameter estimates when estimating separately for (a) families with more than one child and (b) only one child.

Sibling-comparison studies assume that findings from families with multiple offspring generalize to families with only one offspring. Therefore, the interpretation of the sibling-comparison results could be confounded if the population-based associations were different in offspring who had siblings than in those that are only children. If systematic magnitude differences are found between offspring with siblings and only children, then the reduction or increase in association magnitude found in the fixed effects models may be due to alternate explanations.

To help assess whether a bias was introduced by analyzing families with multiple offspring, we estimated the population-based estimates between birth weight and offspring outcomes in (a) offspring without siblings and (b) offspring with siblings. Each figure below presents these two baseline models. One model (grey bars with 95% confidence intervals) estimated on the sub-sample of offspring from families with only one offspring within the dataset. The second model (white bars with 95% confidence intervals) was estimated on the sub-sample of offspring from families with more than one child.

Figures 3A show that the baseline associations are comparable for the two sub-samples of offspring. The figures also suggest that differences between the sub-samples do not account for differences in the sibling-comparison estimates as compared with the population estimates presented in the main paper. Across outcomes, associations in the two sub-samples are in the same direction and the magnitudes of association greatly overlap. Additionally, we found no pattern where magnitudes were always larger in one sub-sample. Overall, this sensitivity analysis suggests that the sibling-comparison results that showed changes in magnitude from the population analyses are not due to different population-based estimates in offspring with siblings than in offspring who are only children.

Figure 3A. Psychiatric Problems

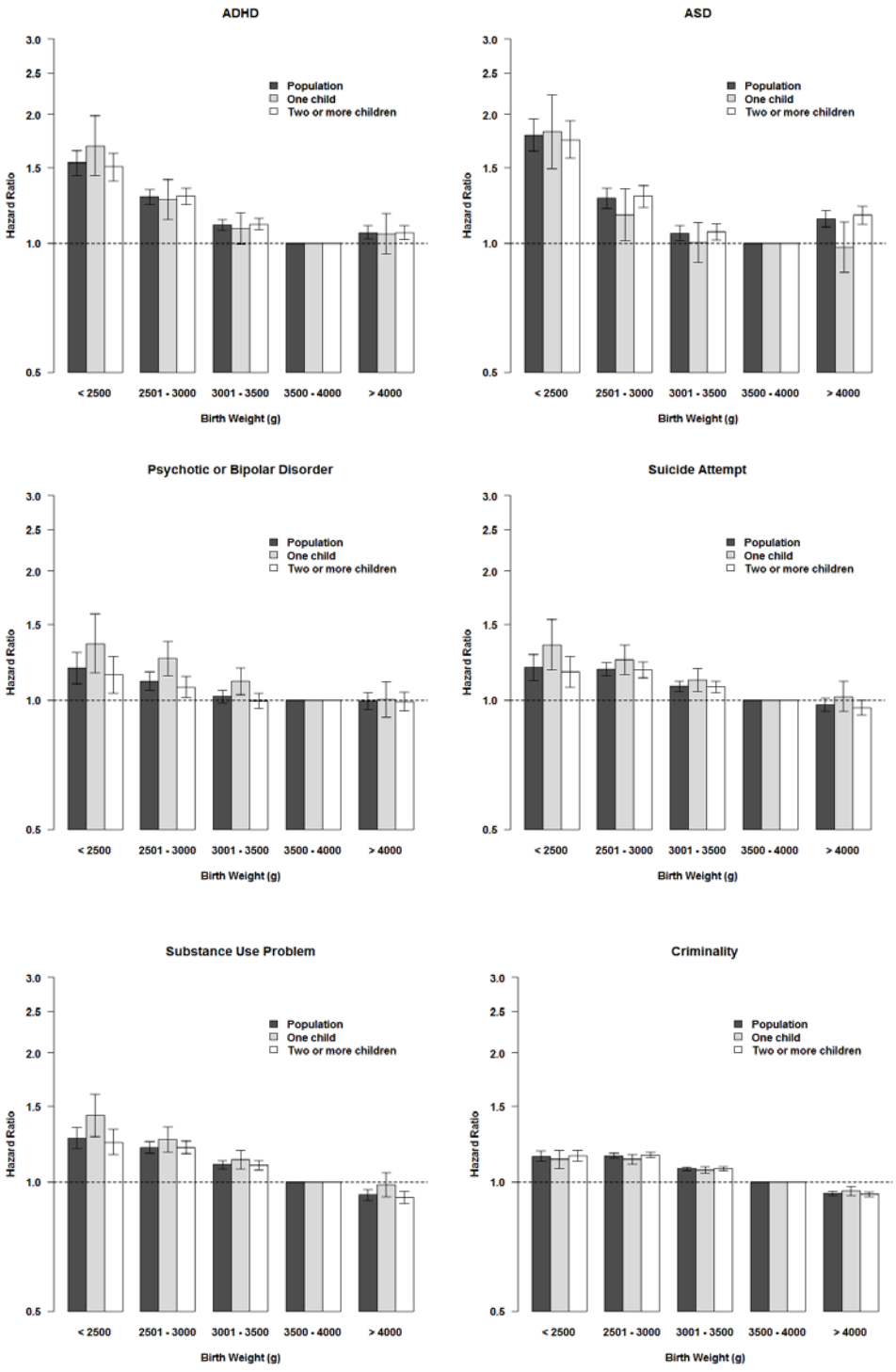


Figure 3A cont. Socioeconomic Outcomes

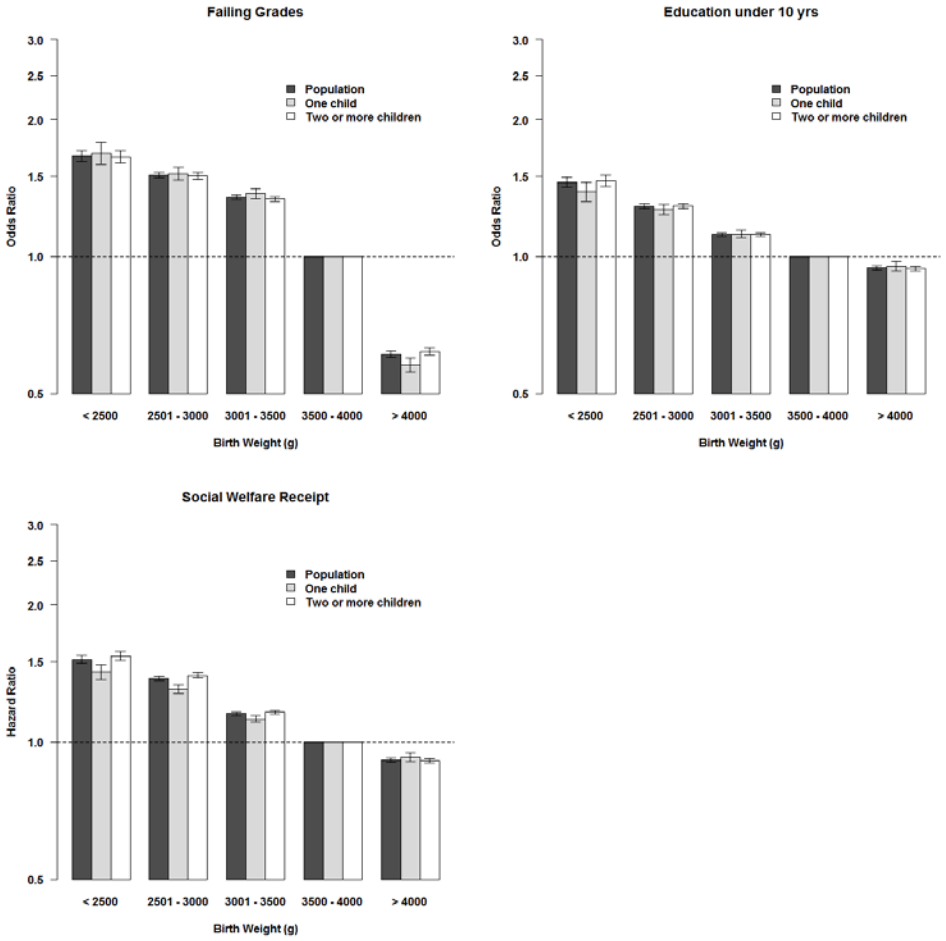


Figure 4A. Fixed effects parameter estimates for cousin comparisons.

To disentangle the source of possible confounding between birth weight and outcome, we conducted another test that utilizes a population that varies in their genetic relatedness. This was important because of inherent assumptions of the sibling-comparison approach, but also because individual genetic factors account for some variability in birth weight [45, 46]. While siblings share 50% of their genetic makeup on average, cousins, share 12.5 % of their genetic makeup on average. Therefore, we examined if the degree to which individuals share genetic risk moderates the association between birth weight and outcomes. If the associations are smaller when comparing relatives that share more genetic background (i.e., sibling associations are smaller than cousin associations), then genetic confounding is implicated. If the associations between birth weight and outcome are found to be the same magnitude across all relative groups, results may instead suggest the importance of environmental confounds. Although cousin versus sibling comparisons cannot by itself support or refute genetic confounding because these groups can also vary on their environmental risk "relatedness", when these results are combined with results from cousin-comparison designs that also vary in the degree of genetic relatedness, more evidence is gathered.

Figure 4A shows baseline, sibling- and cousin-comparison fixed effect (FE) results. Analyses were performed via stratification on the maternal grandmother of the target child. Overall, results for ASD, psychotic or bipolar disorder, and education under 10 years, support the findings that associations are consistent with a causal inference. For suicide attempt, substance use problem, and criminality, sibling and cousin comparisons similarly fully attenuate the association present in the population baseline analysis. For failing grades, social welfare receipt, it can be noted that the magnitudes of association are greater for cousin comparisons than for sibling comparisons, suggesting genetic confounding.

Figure 4A. Comparison of population baseline, fixed effects sibling-comparison, and fixed effect cousin-comparison for psychiatric morbidity and socioeconomic outcomes.

Psychiatric Problems

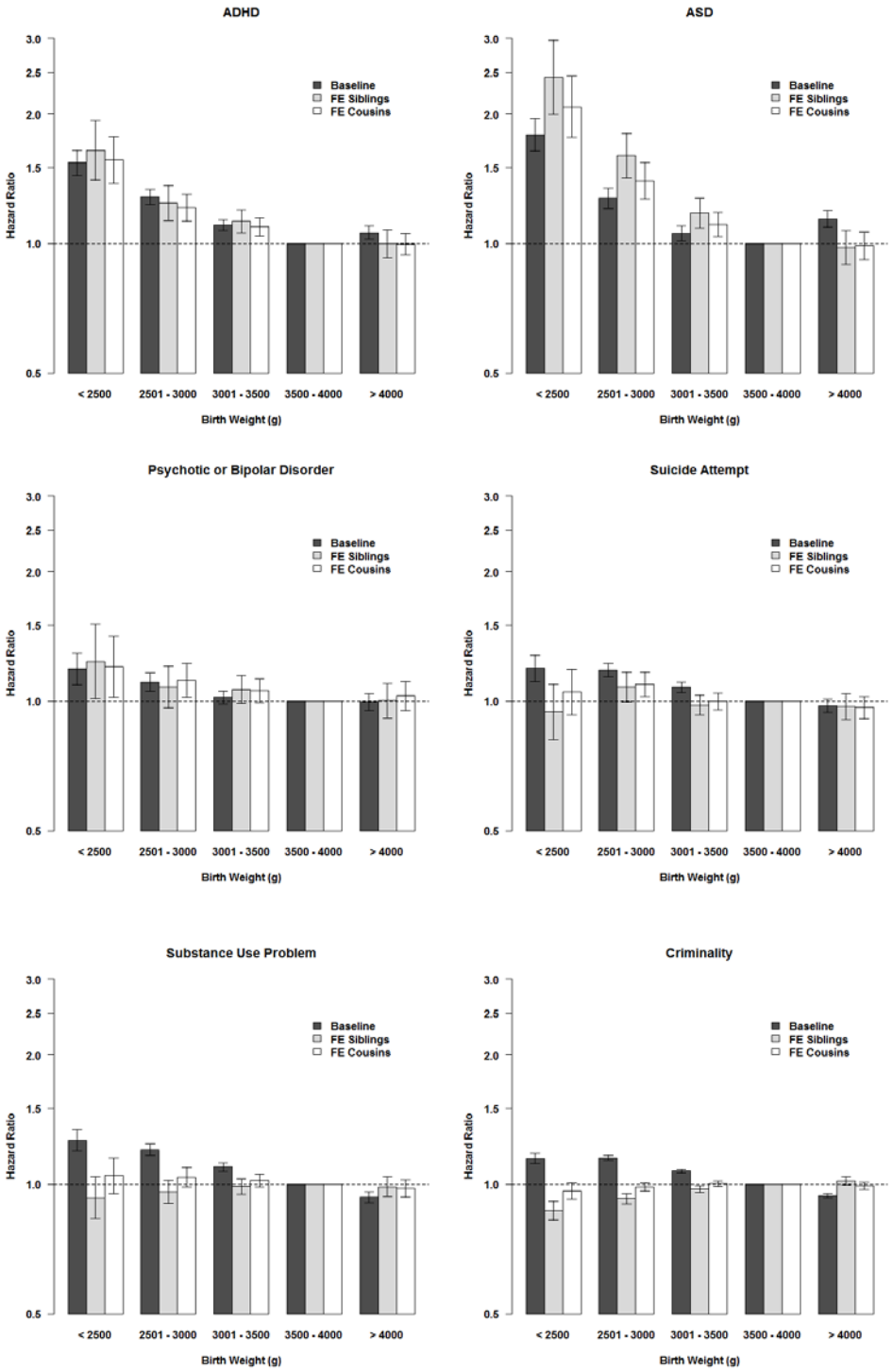
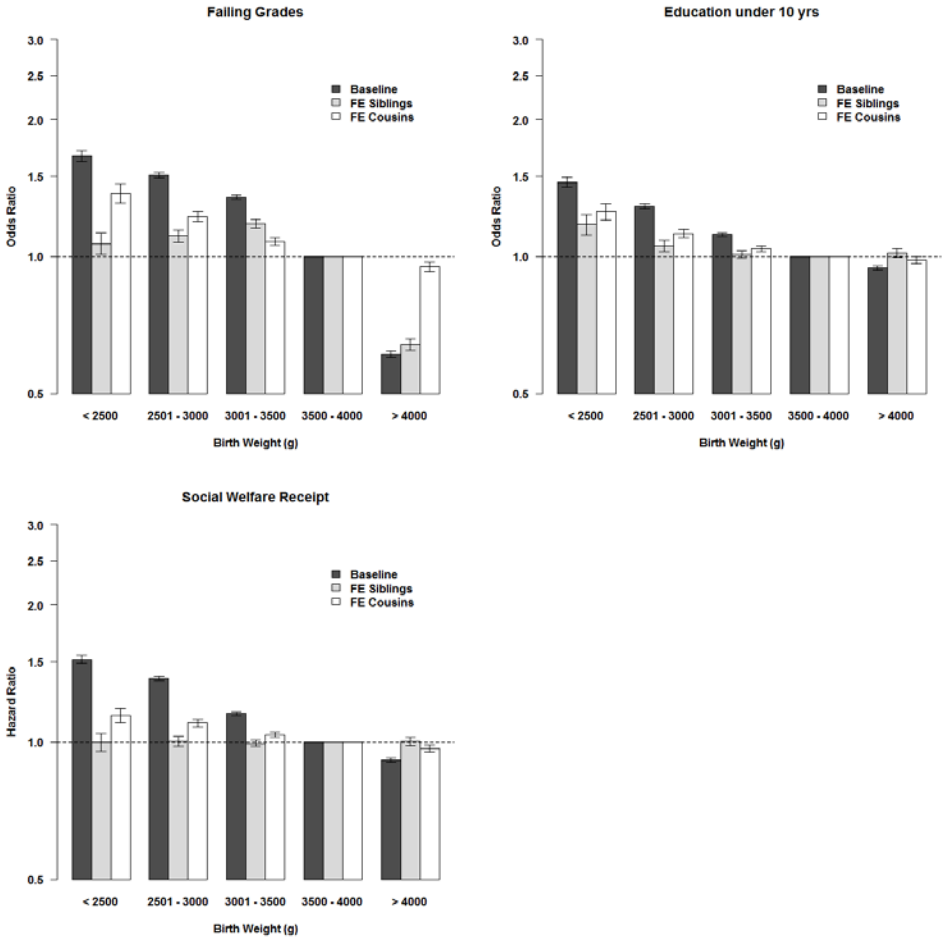


Figure 4A cont. Socioeconomic Outcomes



2.5 Interpregnancy interval predicting adverse birth outcomes

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Abstract

Objective: To test the causal inferences between interpregnancy interval, defined as the duration between birth of the first-born and conception of the second-born, and adverse birth outcomes using an advanced statistical design to control for unmeasured confounding factors.

Design: Using Swedish, population-based data, we utilized logistic regression analyses to predict the odds of preterm birth (≤ 37 weeks), low birth weight (<2,500 g), and small for gestational age (≥ two standard deviations below the average weight for gestational age) from interpregnancy interval in the population, as well as in differentially exposed cousins.

Results: Although risk for preterm birth, low birth weight, and small for gestational age was elevated following short interpregnancy interval (less than 6 months) in population comparisons, only preterm birth was moderately associated with short interpregnancy in cousin-comparisons. Long interpregnancy interval of 72 months or more, however, was robustly predictive of all adverse birth outcomes, even when comparing cousins. Sensitivity analyses, including the comparison of differentially exposed siblings, found commensurate results.

Conclusion: Previous studies may have overestimated the direct effect of short interpregnancy interval on risk for adverse birth outcomes. More research needs to be conducted examining the mechanisms linking long interpregnancy interval and increased odds of adverse birth outcomes because the associations were independent of the measured covariates and confounds shared by cousins.

Interpregnancy interval is the duration between the birth of an earlier born sibling and the conception of the next sibling. Research suggests that deviation from an average interpregnancy interval length of one to three years is associated with adverse offspring outcomes. For example, both short and long interpregnancy intervals are associated with risk for the offspring to be born preterm (≤37 weeks gestation), low birth weight (≤2500 grams), and small for gestational age (≥2 standard deviations below the mean weight for gestational age) [1-6]. Short and long interpregnancy intervals are also associated with the offspring's risk for still birth and infant mortality [6-8]. Decades of research still present mixed findings, however [1, 6, 9, 10]. Some previous research has suggested that the association between short interpregnancy interval and low birth weight [9, 10] and intrauterine growth restriction or small for gestational age births [6], are due to confounding factors. Determining if associations between interpregnancy interval and adverse birth outcomes are independent of confounding factors, consistent with causal inferences, has important public health implications. Interpregnancy interval is a modifiable risk factor [11] and researchers and medical groups have made recommendations about interpregnancy interval with the goal of reducing adverse birth outcomes [1, 12].

Some causal hypotheses linking interpregnancy interval with adverse offspring outcomes have been proposed [for review see 13]. For example, short interpregnancy interval may not allow for adequate restoration of the maternal nutritional foundation [14, 15] or the expression of contraction-related proteins to return to prepregnancy level [16], thereby impacting fetal development. Scar tissue from the first delivery could also contribute to sub-optimal placental implantation during the later pregnancy [6], thereby impeding nutritional transfer from the mother to the fetus. Associations between long interpregnancy interval and adverse offspring outcomes may be explained by an attenuated capacity for the mother to support fetal

development as time passes from her earlier birth because of decreased uterine blood flow or complications related to fertility issues [17].

Though these causal hypotheses exist, small sample sizes, limited control over important covariates, and skewed measurement of interpregnancy interval length (birth to birth rather than birth to conception) [18], have limited the field's ability to draw definitive conclusions. In particular, previous studies have not been able to clarify if the associations are causal or are due to the confounding effects of maternal demographic, fertility, or anatomical issues associated with both interpregnancy interval and adverse offspring outcome, as numerous confounding factors exist [19]. For example, interpregnancy interval varies with maternal age, education, smoking status, and race/ethnic group [7, 20-24]. Within adolescent mothers, poor mental health, trauma history, and behavioral aggression correlate with shorter interpregnancy intervals [21, 25, 26]. Within older mothers, interpregnancy interval has shortened over time [27, 28]. And, medical factors such as diabetes and hypertensive disease [7] and fertility difficulties are correlated with longer interpregnancy intervals [29]. Therefore, the associations between interpregnancy interval and offspring outcomes may be due to many alternative explanations rather than a direct causal relation.

Public health recommendations regarding interpregnancy interval (e.g., with the aim to reduce adverse birth outcomes [12, 30]) are based on strong causal inferences. The current study was designed to provide a rigorous examination of the causal inferences underlying the association between interpregnancy interval and adverse pregnancy outcomes. We used a large, Swedish population-based sample of families, which provided the largest study of the topic to date. First, we examined the degree to which interpregnancy interval is associated with a broad range of maternal and paternal psychiatric, substance use, and socioeconomic factors to better

characterize the families of offspring born after short and long intervals. Second, we estimated the associations between interpregnancy interval and preterm birth, low birth weight, and small for gestational age using various comparisons—we estimated the raw associations in the population, when controlling for measured covariates, and when comparing differentially exposed cousins. The cousin-comparison design rules out all unmeasured environmental and genetic risks that make cousins similar [31]; cousins are more similar on socioeconomic characteristics, familial culture, and genetic factors (i.e., they share 12.5% of their genetic makeup) than unrelated individuals [32]. As such, the increased control over environmental and genetic confounds gained by using a cousin-comparison design provides a rigorous alternative to traditional methods that compare unrelated individuals. Finally, we performed extensive sensitivity analyses to test for alternative explanations.

Methods

Study population

After approval by the Institutional Review Boards at Indiana University and the Karolinska Institutet, data for the current study were obtained by linking information available in the following government-maintained, Swedish population-based registries: (1) the Medical Birth Registry provided data on more than 99% of pregnancies in Sweden since 1973 [33, 34]; (2) the Multi-Generation Register provided biological relationships for all individuals living in Sweden [35]; (3) the Migration Register provided information on dates for migration in or out of Sweden; (4) the Cause of Death Register provided information on dates and causes of all deaths; (5) the National Patient Registry provided diagnoses for all inpatient hospital admissions since 1973 and outpatient care since 2001 [36]; (6) the National Crime Register provided information

on all criminal convictions since 1973 [37]; (7) the National School Register provided grades in all subjects for all students at the end of grade nine since 1983 [38]; (8) the Education Register provided information on highest level of completed formal education through 2008; and finally, (9) the longitudinal integration database for health insurance and social studies (LISA) provided yearly assessments of income, marital status, employment status, social welfare status, and education for all individuals 15 years or older since 1990 [39].

The initial sample included birth-related information for 3,403,185 individuals with valid maternal identifiers born between 1973 and 2008. We removed 74,666 multiple births and 25 individuals with missing parity and only the data for first-, second-, and third- born offspring in each maternal-based nuclear family were retained. We next used the Multi-Generation Register [35] to identify and drop 278,536 individuals whose mother who had at least one child born before 1973 as we did not have detailed birth information on individuals born prior to 1973. We then excluded 13,913 offspring with missing gestational age because this was needed to estimate interpregnancy interval. Following the calculation of interpregnancy interval between the first- and second-born and the second- and third-born offspring in each family, we dropped 1,570,467 first-born offspring from the sample, as they did not have a preceding interpregnancy interval and were therefore not informative. The final cohort consisted of 1,465,578 second- and third-born offspring (i.e., 1,084,777 second-born and 380,801 third-born). The offspring were born to 1,100,045 distinct biological mothers and 1,108,165 distinct biological fathers. There were 797,038 distinct maternal-side grandmothers represented in the cohort used cousin-comparison models.

Measures

Interpregnancy interval

Interpregnancy interval was defined as the number of completed months between the birth of the first-born offspring and the date of conception of the second-born, index offspring. For use in sensitivity analyses, a parallel approach was used to calculate interpregnancy interval between the second- and third-born offspring on the subset of the population with 3 offspring per family. Interpregnancy intervals were categorized as 0 to 5 months, 6 to 11 months, 12 to 23 months, 24 to 35 months (referent), 36 to 71 months, and 72 or more months.

Parental correlates

For both mothers and fathers (the fathers of the second-born, index offspring) we included the following characteristics, which have been shown to be valid indexes of psychiatric, substance use, socioeconomic factors: (1) criminality indexed by the age at first occurrence of any criminal conviction under the Swedish Penal code beginning at age 15, the Swedish age of legal responsibility [40, 41], (2) substance use problem defined as first inpatient hospitalization involving a primary or secondary diagnosis of alcohol- or any other, non-nicotine, substance use disorder [42], (3) death by suicide as indicated by the cause of death record [43], (4) suicide attempt as indicated by the age at first attempt recorded in inpatient care records as the a primary or secondary reason for care [43], and (5) severe mental illness as measured by the age at the first inpatient hospitalization for bipolar disorder, broadly defined schizophrenia, or other nonorganic psychotic disorders [44]. Except for criminality, the minimum age for all parental mental health outcomes was 12 years old. All clinical diagnoses were according to versions 8, 9, and 10 of the International Classification of Diseases (ICD) and are presented in the Appendix, Table 1A.

We also predicted several dichotomized maternal, paternal and offspring-specific socioeconomic and demographic factors including, (1) maternal and paternal nationality

measured as Swedish or non-Swedish, (2) maternal and paternal low education as indexed by education under 10 years equating to primary or lower secondary education, (3) first birth occurred while the mother was teenager defined as greater than or equal to age 13 years and less than 20 years, (4) the first and second offspring have different fathers, (5) the parents were not cohabitating at the time of birth of the second born, index offspring, (6) the first born was born preterm (<37 weeks of gestation), and (7) the first born was born low birth weight (<2500 g).

Offspring outcomes

We predicted 3 adverse birth outcomes in the second-born, index offspring. Preterm birth was defined as birth <37 weeks of gestation. Low birth weight was defined as birth weight of <2500 g and birth weights were considered erroneous and removed from analyses if <500 or >6000 g. In accordance with Swedish weight-based growth standards [45], small for gestational age was defined as a birth weight of 2 standard deviations below the mean for gestational age.

Statistical Analyses

Parental correlates

We calculated the associations between interpregnancy interval and parental psychiatric, substance use, and socioeconomic variables using Cox survival analyses for right-censored variables (i.e., parental psychiatric and substance use outcomes) and logistic regression for dichotomous parental variables. For the survival analyses, if parents had not received a diagnosis within the study period, they contributed person-time at risk until death, emigration, or the end date of follow-up (December 31, 2009), whichever came first.

Offspring outcomes

For offspring adverse birth outcomes, we used logistic regression analyses accounting for family clustering when predicting the second-born, index offspring's outcomes. The first model

was a baseline model and only adjusted for offspring sex and year of birth. The second model adjusted for offspring sex, year of birth, and all of the measured covariates from the previous section, including all previously mentioned parental psychopathology variables, maternal and paternal nationality, maternal and paternal highest level of completed education, maternal and paternal age at birth, if the father of the second-born index offspring was the same as the father of the first-born offspring, whether the parents were cohabitating, if the first-born was born premature, and if the first-born was born low birth weight. Dummy coding was used to handle missing covariate information. The final, most rigorous model, utilized fixed-effects analysis clustering at the grandmother maternal level [46, 47]. The third model, therefore, compared cousins with different interpregnancy interval lengths and included all above mentioned offspring-specific and parental covariates, as they may have varied between cousins. Thus, the model controlled for all genetic and environmental factors shared among first cousins [31], as well as the influence of all of the covariates.

Sensitivity analyses

We ran sensitivity analyses to (1) test the assumptions and strength of findings from the cousin-comparison using a more rigorous sibling-comparison in a subsample of our population, (2) explore if risk associated with interpregnancy interval is specific for the interval prior to the second-born offspring by utilizing the post-pregnancy interpregnancy interval (the interval between the second- and third-born offspring) to predict the outcomes in the second-born offspring, (3) sought converging evidence by predicting continuously measured gestational age, birth weight, and birth weight controlling for gestational age, and (4) explored the predictive value of the first-born's adverse birth outcomes (i.e., preterm birth and low birth weight) by performing all analyses without these covariates.

Results

Table 1 presents demographic information for the second-born offspring.

Parental correlates

Figure 1 presents the hazard ratios (HR) with 95% confidence intervals (CI) between interpregnancy interval and maternal (left panel) and paternal (right panel) psychiatric and substance use variables. As seen in Figure 1, all measured forms of parental psychopathology are associated with both short and long interpregnancy intervals as compared with the reference interpregnancy interval category of 24-35 months. For example, parents with the shortest interpregnancy intervals (0-5 months) were approximately twice as likely to attempt suicide ($HR_{maternal}$=2.27, 95% CI=2.26-2.40; $HR_{paternal}$=2.11, 95% CI=1.98-2.26) over the course of their lifetime. Similar increased risk was found between the longest interpregnancy interval (72 months or more) and suicide attempt, ($HR_{maternal}$=1.98, 95% CI=1.91-2.05; $HR_{paternal}$=1.67, 95% CI=1.59-1.75). All of the point estimates and confidence intervals are presented in the Appendix Table 2A.

Figure 2 presents the associations between interpregnancy interval and parental socioeconomic information as odds ratios (OR) with 95% CI. As can be seen in Figure 2, for example, mothers with low education were over three times more likely to have a second child 0-5 months after the birth of their first child (OR=3.30, 95% CI=3.13-3.48). Families with the shortest interpregnancy intervals were also less likely to be of Swedish nationality ($OR_{maternal}$=0.32, 95% CI=0.31-0.32; $OR_{paternal}$=0.33, 95% CI=0.32-0.34). The longest interpregnancy intervals, of 72 months or longer, were characterized by an almost 35 times increased odds the fathers of the first and second offspring are different men (OR=34.95, 95% CI=34.07-35.85), among other characteristics prominent in the figure. Appendix Table 2A

presents all point estimates between interpregnancy interval and parental socioeconomic outcomes. In sum, it should be noted that all studied parental psychiatric, substance use, and socioeconomic factors were highly related to both short and long interpregnancy interval lengths.

Offspring outcomes

Figure 3 presents the results, in the form of OR with 95% CI, from baseline (red line, square points), adjusted (green line, circle points), and fixed-effect cousin-comparison analyses (blue line, triangle points) across adverse birth outcomes. The pattern of findings for adverse birth outcomes was outcome-specific. As reported in Table 2, short IPI was associated with preterm birth in baseline model (e.g., $OR_{0\text{-}5months}$=1.87, 95% CI=1.78-1.97), and the magnitude was attenuated, albeit still robust, in the adjusted model ($OR_{0\text{-}5months}$=1.32, 95% CI=1.25-1.39). Although further attenuated, the association remained in fixed-effects model for the shortest interpregnancy interval group of 0 to 5 months (OR=1.27, 95% CI=1.17-1.37). The association between the longest interpregnancy interval category of 72 months of more, showed a parallel pattern when predicting preterm birth. That is, the association was present in the baseline model (OR=1.77, 95% CI=1.70-1.83), attenuated in the adjusted model (OR=1.45, 95% CI=1.39-1.52), and further attenuated, though robust, in the fixed-effects model (OR=1.23, 95% CI=1.16-1.32).

In contrast, although short interpregnancy interval predicted increased risk for low birth weight in the baseline model (OR=1.73, 95% CI=1.62-1.85), the association was greatly reduced in adjusted models (OR=1.10, 95% CI=1.03-1.18), and not present in the fixed effects cousin-comparison model (OR=0.96, 95% CI=0.87-1.06). The relation between long interpregnancy interval and low birth weight, however, was robust in the baseline (OR=2.02, 95% CI=1.94-2.12), adjusted (OR=1.55, 95% CI=1.47-1.63), and fixed-effects models (OR=1.47, 95% CI=1.35-1.59).

Models predicting small for gestational age also presented a distinct pattern of association. The increased odds of small for gestational age in the baseline model for the shortest interpregnancy interval (OR=1.33, 95% CI=1.23-1.43) was not robust after adjustment (OR=0.94, 95% CI=0.86-1.01) and was slightly protective against small for gestational age in the fixed-effects model (OR=0.74, 95% CI=0.65-0.83), similar to the results with interpregnancy interval of 6-11 months. Parallel to the relation between the longest interpregnancy interval and the other adverse birth outcomes, an interpregnancy interval of 72 months or longer was associated with an increased odds of small for gestational age in baseline (OR=1.84, 95% CI=1.74-1.93), adjusted (OR=1.43, 95% CI=1.35-1.52), and fixed-effects models (OR=1.40, 95% CI=1.28-1.54).

Sensitivity analyses

We first performed sibling-comparison analyses to further test the strength of significant associations and generally found commensurate results to the cousin-comparisons. A sibling-comparison is more rigorous than a cousin-comparison because the analysis controls for all factors that make siblings similar, shared environmental factors and the 50% genetic similarity of siblings (as compared to the 12.5% genetic similarity of first cousins) [32]. Our sibling-comparison analysis compared the rates of outcome between the second- and third-born offspring if their interpregnancy interval categories differed. There were a total of 380,801 third-born offspring. We found that the increased odds of preterm birth following the shortest interpregnancy interval was further attenuated, though an elevated risk was still evident (OR=1.19, 95% CI=1.09-1.30). The protective effect found between the shortest interpregnancy interval and small for gestational age in the cousin-comparisons was robust (OR=0.68, 95% CI=0.60-0.77) in sibling-comparisons and paralleled in low birth weight (OR=0.82, 95%

CI=0.74-0.91). Following the longest interpregnancy interval of 72 months of more, sibling-comparison analyses further attenuated the associations with preterm birth (OR=1.09, 95% CI=1.00-1.18), low birth weight (OR=1.28, 95% CI=1.15-1.42), and small for gestational age (OR=1.38, 95% CI=1.22-1.56), though elevated magnitudes were still identified. Results across all interpregnancy intervals in sibling-comparison analyses are available in the Appendix Table 3A.

We next explored the relation between the post-pregnancy interpregnancy interval, meaning the interval between the second- and third-born offspring, and adverse birth outcomes for the second-born, index offspring. Performed on the main sample of 1,084,777 second-born offspring using dummy-coded post-pregnancy intervals including if the family did not have a third-born offspring, this sensitivity analysis was used to further examine the causal inferences of interpregnancy interval. In adjusted analyses, we found that the odds of preterm birth (OR=2.57, 95% CI=2.38-2.77), low birth weight (OR=2.97, 95% CI=2.72-3.25), and small for gestational age (OR=2.11, 95% CI=1.90-2.34) was approximately double if the post-pregnancy interval was short (0-5 months). A long post-pregnancy interval (72 or more months) was very minimally associated with the second born, index offspring being preterm (OR=1.10, 95% CI=1.03-1.17), and not associated with low birth weight (OR=1.04, 95% CI=0.96-1.12), or small for gestational age (OR=1.02, 95% CI=0.94-1.11). Results across all interpregnancy intervals in post-pregnancy interpregnancy interval analyses are available in the Appendix Table 4A.

We then predicted continuously measured gestational age, birth weight, and birth weight while controlling for gestational age. Findings were commensurate to those predicting ordinal adverse birth outcomes. There was a small decrease in gestational length, even in cousin-comparisons, associated with the shortest interpregnancy intervals. The longest interpregnancy

intervals showed consistent increase risk for all adverse birth outcomes. The results are presented in the Appendix Figure 1A.

Finally, we removed first-born preterm or low birth weight indicators from the adjusted and cousin-comparison models to explore the predictive role of adverse birth outcomes within a family. Association magnitudes were comparable to main analyses, though slightly elevated without these additional covariates. Interpretations of the results were the same as in main analyses. Results are presented in the Appendix Table 5A.

Discussion

Using Swedish population data, we explored the relation between interpregnancy interval between the first-and second-born offspring and birth outcomes in the second-born offspring. By using several quasi-experimental designs that account for unmeasured confounds while also continuing to adjust for measured covariates, we tested the causal inferences previously suggested between interpregnancy interval and adverse birth outcomes [9, 13].

In the population, baseline analyses between short and long interpregnancy intervals increased the risk for all adverse birth outcomes, supporting previous meta-analytic conclusions [1]. We noted that parental psychiatric, socioeconomic, and demographic factors were highly associated with interpregnancy interval and therefore controlled for these factors in adjusted analyses. We found that adjusted analyses for shorter interpregnancy intervals (less than 24 months) were greatly attenuated for preterm birth and low birth weight. Associations between shorter interpregnancy intervals and small for gestational age were fully attenuated after adjusting for measured covariates. For longer interpregnancy intervals (longer than 36 months), associations across for all outcomes were greatly attenuated.

In cousin-comparisons, however, short interpregnancy interval only predicted an increased risk for preterm birth, not low birth weight or small for gestational age. In fact, short interpregnancy interval appeared to be protective against small for gestational age and low birth weight. Sensitivity analyses supported these conclusions. Previous work has also presented reduced magnitudes of association for low birth weight after adjustment [6]. Other epidemiological studies have shown that risk between short interpregnancy interval and low birth weight and small for gestational age is eliminated or changes directionality after controlling for measured covariates [10], whereas the association with preterm birth is robust [6, 9].

The small specific link between short interpregnancy interval and increased odds of preterm birth may not be due to maternal nutritional depletion [14, 15] or sub-optimal implantation of the placenta [16], because these mechanisms would likely influence all three outcomes in the same, negative direction. Rather, the mechanism that may be driving the small independent association between short interpregnancy interval and preterm birth may be a failure of contraction-related proteins to return to prepregnancy levels [6, 48], though more research is needed.

Long interpregnancy interval (72 months or more) robustly predicted increased risk for preterm birth, low birth weight, and small for gestational age even in cousin-comparisons. The sensitivity analyses, sibling-comparisons, post-pregnancy interval, continuously measured outcomes, and not adjusting for first-born birth outcomes, also supported the specific effect of long interpregnancy interval on adverse birth outcomes. A large meta-analysis [1] has previously shown increased risk for adverse birth outcomes following a long interpregnancy interval. While more research is needed on potential mechanisms, it has been suggested that there is a gradual decline in reproductive capacity following a birth [17]. The gradual physiological regression

contributes to the parous woman presenting a similar birth outcome profile to a primigravid woman [17]. Alternatively, or perhaps in conjunction, infections may contribute to both fertility issues, thereby lengthening the interpregnancy interval, as well as increasing adverse pregnancy outcomes [17]. Future research would also benefit from exploring the role of breastfeeding in this complex association, as breastfeeding has been shown to elongate the interpregnancy interval but also further deplete maternal nutrient stores [8].

As alluded to in the above paragraphs, we conducted several sensitivity analyses to test for alternative explanations. We first conducted a sibling-comparison. The sibling-comparison design accounts for more genetic and environment confounds and the design has different limitations (e.g. potential for carry-over effects) than the cousin-comparison design [32]. Yet, both designs resulted in the same conclusions. In particular, the only specific effect with short interpregnancy interval was for preterm birth, although the magnitude of the association was smaller than estimates comparing unrelated individuals and when controlling for measured covariates. Short interpregnancy interval was associated with lower odds of low birth weight and small for gestational age in both designs. Second, we examined the role of the post-pregnancy interval on the prior-born, index child's adverse birth outcomes (i.e., we examined the associations between the interval between the second- and third-born child with adverse birth outcomes in the second-born offspring). We found an increased association with preterm birth, low birth weight, and small for gestational age with short post-pregnancy intervals, suggesting familial factors largely account for the association. Previous research has shown that a prior preterm, low birth weight, or small for gestational age baby is associated with shorter post-pregnancy intervals [1, 6, 10], which may explain some of the positive association between a prior born child and an increase risk with the following interpregnancy interval length. Third, we

performed analyses predicting continuously measured birth outcomes and results supported our main analysis conclusions. Finally, we removed first-born preterm and first-born low birth weight covariates from the models. Conclusions were, yet again, the same.

Important for future research, we expanded on previous work showing the numerous factors that are correlated with interpregnancy interval [7, 20-29]. In the current study, we found that maternal and paternal psychopathology, including criminality, death by suicide, suicide attempt, substance use problem, and broadly defined severe mental illness, were associated with increased odds of short and long interpregnancy interval. If the parents were not of Swedish nationality, there was decreased odds that they would conceive a child after a short or long interpregnancy interval. Maternal and paternal low educational achievement, the first birth occurring when the mother was a teenager, parental cohabitation status at childbirth, and if the first-born child was preterm or low birth weight were also associated with increased odds of short or long interpregnancy intervals. Additionally, the longer the interpregnancy interval, the more likely the first and second born had different fathers. Given the high level of association between both short and long interpregnancy interval and potentially confounding factors, taking a quasi-experimental approach to studying interpregnancy interval is necessary to draw causal inferences from the results.

While we capitalize on our large, rich dataset by using advanced statistical design to draw causal inferences, several limitations must be considered. Various factors may influence the generalizability of our findings. Due to the relative ethnic homogeneity of the Swedish population, future research should perform quasi-experimental analyses across ethnic and racial groups [22-24]. Similarly, prenatal care is advanced and comprehensive in Sweden. This may have influenced both interpregnancy interval length and birth outcomes [30]. Thus, replication in

different populations is needed. We used a variety of quasi-experimental designs to help address limitations inherent in each of the designs. For example, using a cousin-comparison allowed us to compare related individuals that were the same parity (i.e., second-born), something that could not have been possible in a sibling-comparison. Nevertheless, cousin- (and sibling-) comparisons are not randomized controlled studies; therefore, the design cannot rule out all possible confounding factors and causation cannot be proven [32, 49].

Our findings suggest that modification to increase the interpregnancy interval (i.e., reducing short interpregnancy interval) will only have a minimal effect on reducing the likelihood of preterm birth and may not influence risk for low birth weight or small for gestational age. Our findings also suggest that unusually long interpregnancy intervals have a specific effect of increasing the odds of adverse birth outcomes. More research into the mechanisms driving these associations is necessary to direct intervention/prevention efforts for this risk factor.

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Table 1. Descriptive characteristics and covariates for the index, second-born offspring

Variable	Index Second-Born n (%)
n	1084777
Interpregnancy Interval (months)	
0-5	31882 (2.9)
6-11	133348 (12.3)
12-23	378088 (34.9)
24-35*	239506 (22.1)
36-71	2233574 (20.6)
72+	78379 (7.2)
Maternal Age (yrs)	
< 24	195838 (18.1)
25-29*	428614 (39.5)
30-34	337907 (31.2)
≥35	122418 (11.3)
Paternal Age (yrs)	
Missing	7501 (0.7)
< 24	73623 (6.8)
25-29*	329976 (30.4)
30-34	396776 (36.6)
≥35	276901 (25.5)
Maternal Highest Education	
Missing	5928 (0.6)
≤ 9 yrs	112816 (10.40)
1-3 yrs upper secondary*	529763 (48.8)
Post-secondary	436270 (40.22)
Paternal Highest Education	
Missing	13480 (1.2)
≤ 9 yrs	181987 (16.8)
1-3 yrs upper secondary*	539758 (49.8)
Post-secondary	349552 (32.2)
Maternal Swedish Nationality*	957697 (88.3)
Paternal Swedish Nationality*	950541 (87.6)
Missing	7501 (0.7)
Maternal Psychopathology	
Criminality	115630 (10.7)
Death by suicide	1065 (0.1)
Attempted suicide	24405 (2.3)
Substance use problem	18434 (1.7)
Severe mental illness	15554 (1.4)
Paternal Psychopathology	
Criminality	319930 (29.5)
Death by suicide	3357 (0.3)
Attempted suicide	16601 (1.5)
Substance use problem	33903 (3.1)
Severe mental illness	14268 (1.3)
Parents Not Cohabitating	85223 (7.9)
Missing	70040 (6.5)
First- and Second-born have Different Fathers	95015 (8.8)
Missing	17460 (1.6)

Table 2. Odds ratios of interpregnancy interval predicting second-born adverse birth outcomes across statistical models

Outcome Variable and Model	Interpregnancy Interval (months)										
	0-5		6-11		12-23		24-35	36-71		72+	
	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	OR	95% CI
Preterm birth											
Baseline	1.87	1.78-1.97	1.12	1.09-1.16	0.95	0.92-0.97	ref	1.24	1.20-1.28	1.77	1.70-1.83
Adjusted	1.32	1.25-1.39	1.07	1.03-1.11	0.96	0.93-0.99	ref	1.16	1.13-1.20	1.45	1.39-1.52
Cousin-comparison	1.27	1.17-1.37	1.11	1.05-1.17	1.00	0.95-1.04	ref	1.07	1.02-1.12	1.23	1.16-1.32
Low birth weight											
Baseline	1.73	1.62-1.85	1.03	0.98-1.08	0.92	0.89-0.95	ref	1.32	1.28-1.37	2.02	1.94-2.12
Adjusted	1.10	1.03-1.18	0.95	0.91-1.00	0.93	0.90-0.97	ref	1.20	1.15-1.24	1.55	1.47-1.63
Cousin-comparison	0.96	0.87-1.06	0.98	0.91-1.06	1.00	0.95-1.06	ref	1.12	1.05-1.19	1.47	1.35-1.59
Small for gestational age											
Baseline	1.33	1.23-1.43	0.88	0.83-0.92	0.90	0.86-0.93	ref	1.24	1.19-1.29	1.84	1.74-1.93
Adjusted	0.94	0.86-1.01	0.82	0.78-0.87	0.91	0.88-0.95	ref	1.12	1.08-1.17	1.43	1.35-1.52
Cousin-comparison	0.74	0.65-0.83	0.82	0.75-0.89	0.95	0.89-1.02	ref	0.99	0.93-1.06	1.40	1.28-1.54

Figure Legend.

Figure 1. U-shaped relation in the hazard ratios of maternal (top) and paternal (bottom) psychopathology across interpregnancy interval between the first and second born child. Reference interpregnancy interval ranged from 24-35 months.

Figure 2. Odds ratios of numerous parental socioeconomic and demographic characteristics across interpregnancy intervals between the first- and second-born offspring. Reference interpregnancy interval ranged from 24-35 months.

Figure 3. Odds ratios of (a) preterm birth, (b) low birth weight, and (c) small for gestational age across interpregnancy interval between the first- and second-born offspring in baseline (red line and square points), adjusted (green line and circle points), and fixed-effect cousin-comparison analyses (blue line and triangle points). Reference interpregnancy interval ranged from 24-35 months.

Figure 1.

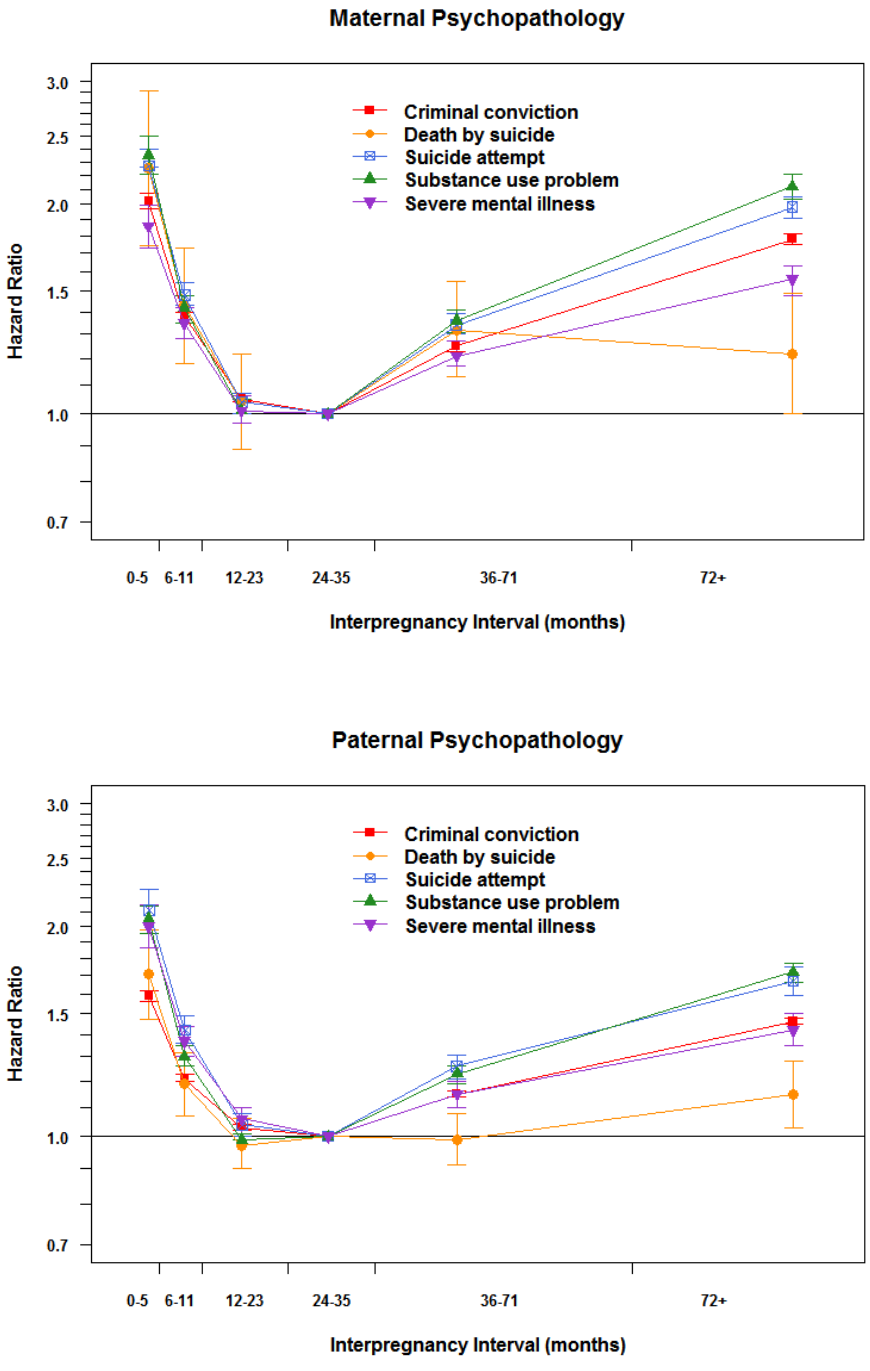

Maternal Psychopathology
Criminal conviction
Death by suicide
Suicide attempt
Substance use problem
Severe mental illness
Hazard Ratio
3.0
2.5
2.0
1.5
1.0
0.7
0-5
6-11
12-23
24-35
36-71
72+
Interpregnancy Interval (months)
Paternal Psychopathology
Criminal conviction
Death by suicide
Suicide attempt
Substance use problem
Severe mental illness
Hazard Ratio
3.0
2.5
2.0
1.5
1.0
0.7
0-5
6-11
12-23
24-35
36-71
72+
Interpregnancy Interval (months)

Figure 2.

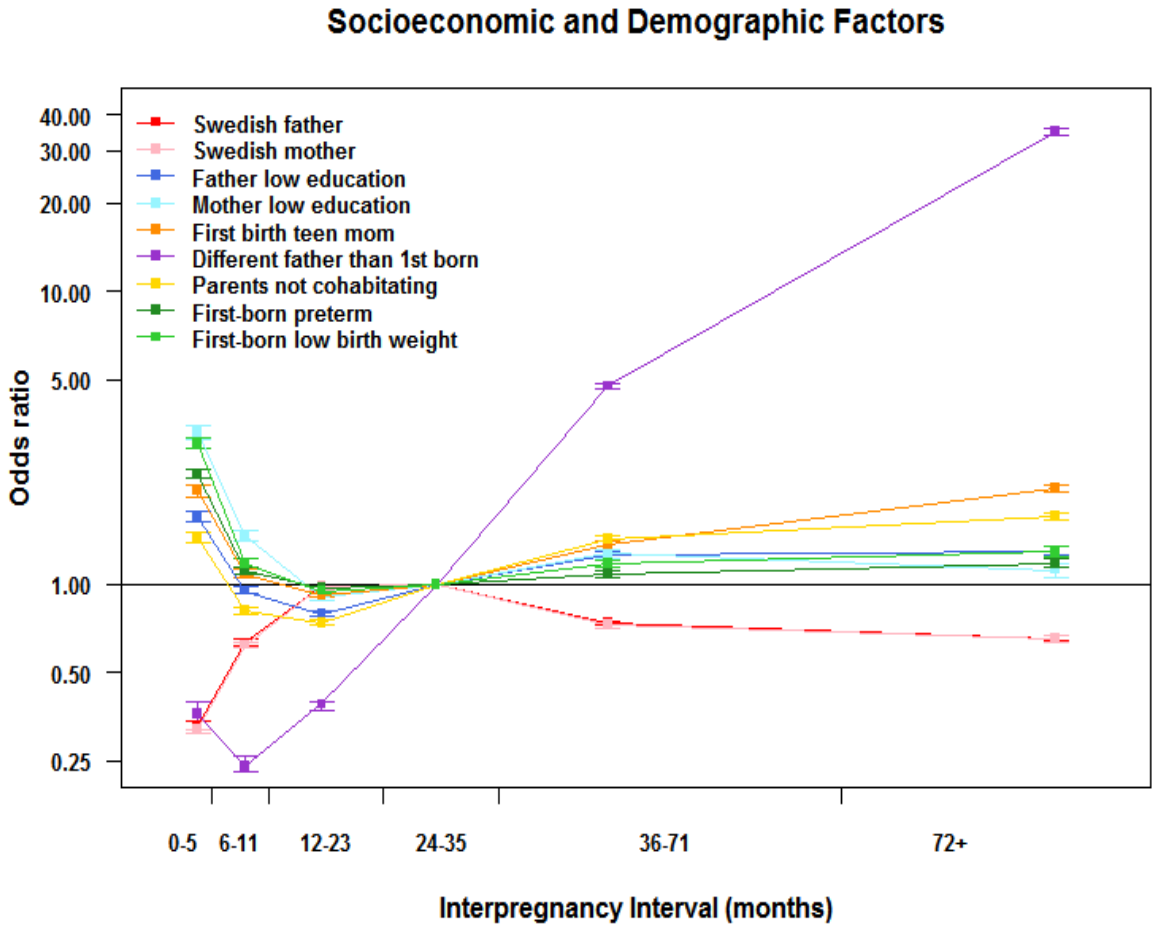
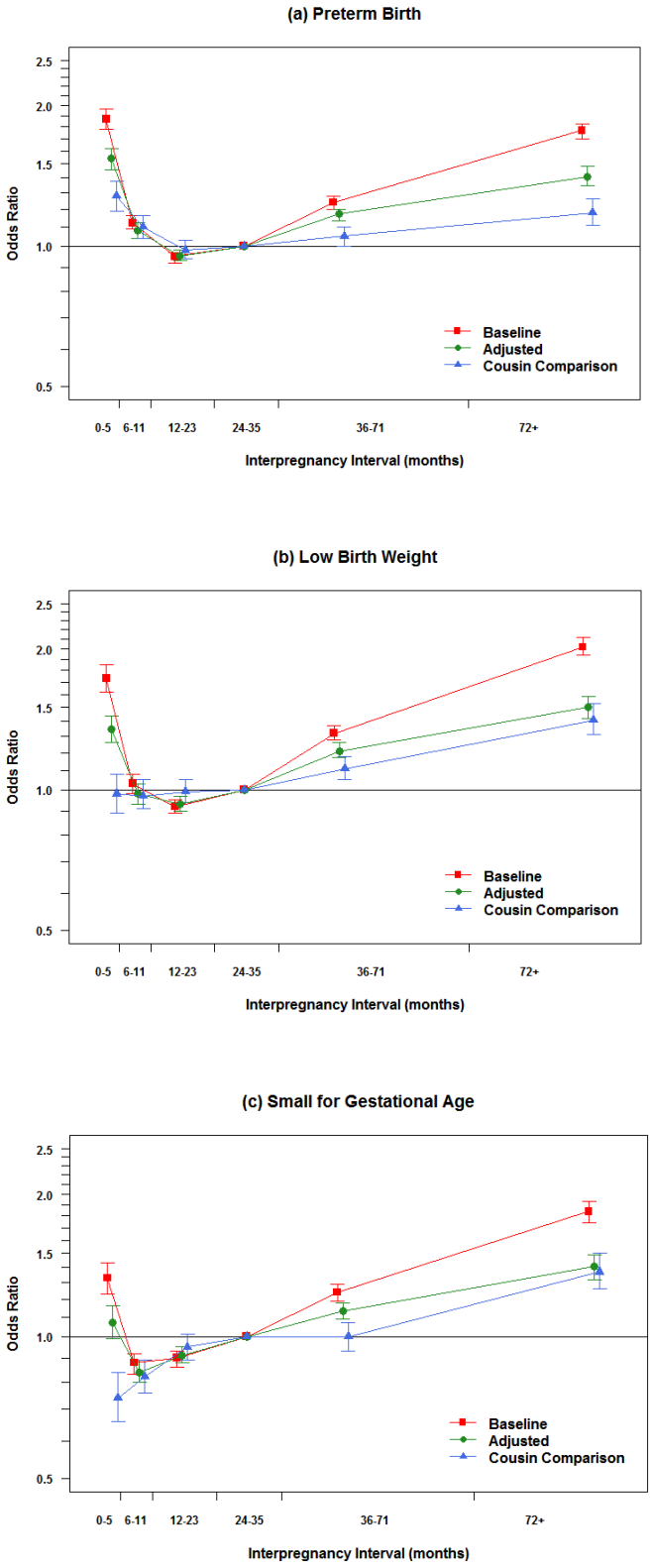

Socioeconomic and Demographic Factors
Swedish father
Swedish mother
Father low education
Mother low education
First birth teen mom
Different father than 1st born
Parents not cohabitating
First-born preterm
First-born low birth weight
Odds ratio
40.00
30.00
20.00
10.00
5.00
1.00
0.50
0.25
0-5
6-11
12-23
24-35
36-71
72+
Interpregnancy Interval (months)

Figure 3.


(a) Preterm Birth
Odds Ratio
2.5
2.0
1.5
1.0
0.5
Baseline
Adjusted
Cousin Comparison
0-5
6-11
12-23
24-35
36-71
72+
Interpregnancy Interval (months)
(b) Low Birth Weight
Odds Ratio
2.5
2.0
1.5
1.0
0.5
Baseline
Adjusted
Cousin Comparison
0-5
6-11
12-23
24-35
36-71
72+
Interpregnancy Interval (months)
(c) Small for Gestational Age
Odds Ratio
2.5
2.0
1.5
1.0
0.5
Baseline
Adjusted
Cousin Comparison
0-5
6-11
12-23
24-35
36-71
72+
Interpregnancy Interval (months)

Appendix: Interpregnancy interval predicting adverse birth outcomes

Table of Contents

Table 1A. International Classification of Disease (ICD) version and codes used to measure parental psychiatric and substance use outcomes

Outcome	Data Source	ICD Version	ICD Codes	Description
Criminality	NCR	NA	NA	Earliest conviction for any criminal act, minimum age of 15 yrs
Death by suicide	COD	NA	NA	Certain and uncertain suicide as primary cause of death
Suicide attempt	NPR	8, 9, 10	E950-E959, E980-E989, X60-X84, Y870, Y10-Y34, Y872	Certain and uncertain attempts including violent, non-violent, and other
Substance use problem	NPR	8, 9, 10	303, 304, 305A, 305X, F10 (except x.5), F11-F19 (except x.5)	Alcohol or drug use (excludes nicotine) conviction
Severe mental illness	NPR	8, 9, 10	295, F20	Schizophrenia
			296.1, 296.3, 296A-296E, 296W, F30-F31	Bipolar disorder
			291, 292, 296.0, 296.2, 296.9, 297-299, 296B, 296X, F32.3 x.5 in F10-F19	Other non-organic psychoses

Note: NCR = National crime register, COD = Cause of death register, PR = Patient register

Table 2A. Hazard and odds ratios of interpregnancy interval predicting parental psychiatric, substance use, and socioeconomic factors

	Interpregnancy Interval (months)										
	0-5		6-11		12-23		24-35	36-71		72+	
Outcome Variable	HR/OR	95% CI	HR/OR	95% CI	HR/OR	95% CI		HR/OR	95% CI	HR/OR	95% CI
Maternal Psychopathology											
Criminality	2.02	1.97-2.07	1.38	1.35-1.40	1.05	1.04-1.07	ref	1.25	1.23-1.27	1.78	1.75-1.81
Death by suicide	2.25	1.74-2.91	1.43	1.18-1.73	1.04	0.89-1.22	ref	1.32	1.13-1.55	1.22	1.00-1.49
Suicide attempt	2.27	2.26-2.40	1.48	1.43-1.54	1.04	1.00-1.07	ref	1.34	1.30-1.39	1.98	1.91-2.05
Substance use problem	2.35	2.21-2.50	1.42	1.35-1.48	1.01	0.97-1.05	ref	1.36	1.31-1.41	2.12	2.03-2.21
Severe mental illness	1.86	1.73-1.99	1.35	1.28-1.42	1.01	0.97-1.06	ref	1.21	1.17-1.27	1.56	1.48-1.63
Paternal Psychopathology											
Criminality	1.59	1.56-1.62	1.21	1.20-1.23	1.03	1.02-1.04	ref	1.15	1.14-1.16	1.46	1.45-1.48
Death by suicide	1.71	1.47-1.98	1.19	1.07-1.32	0.97	0.90-1.06	ref	0.99	0.91-1.08	1.15	1.03-1.28
Suicide attempt	2.11	1.98-2.26	1.42	1.36-1.49	1.04	1.00-1.08	ref	1.26	1.21-1.31	1.67	1.59-1.75
Substance use problem	2.05	1.95-2.14	1.30	1.26-1.35	0.99	0.99-1.01	ref	1.23	1.19-1.26	1.72	1.66-1.77
Severe mental illness	2.00	1.86-2.15	1.37	1.30-1.44	1.06	1.01-1.10	ref	1.15	1.10-1.20	1.42	1.35-1.50
Socioeconomic Factors											
Mother Swedish nationality	0.32	0.31-0.32	0.62	0.61-0.63	0.98	0.96-0.99	ref	0.73	0.71-0.74	0.65	0.63-0.67
Father Swedish nationality	0.33	0.32-0.34	0.63	0.62-0.65	0.98	0.96-0.99	ref	0.74	0.73-0.75	0.65	0.64-0.67
Mother low education	3.30	3.13-3.48	1.46	1.40-1.52	0.91	0.88-0.95	ref	1.27	1.22-1.32	1.12	1.06-1.18
Father low education	1.71	1.64-1.78	0.95	0.93-0.98	0.79	0.78-0.81	ref	1.26	1.23-1.30	1.30	1.26-1.34
First birth as teenager	2.08	1.99-2.17	1.09	1.06-1.13	0.92	0.90-0.95	ref	1.36	1.32-1.40	2.11	2.05-2.18
Different father than 1st born	0.36	0.32-0.40	0.24	0.23-0.26	0.39	0.37-0.40	ref	4.74	4.63-4.85	34.95	34.07-35.85
Parents not cohabitating	1.45	1.39-1.51	0.81	0.79-0.83	0.74	0.73-0.76	ref	1.43	1.40-1.46	1.70	1.65-1.75
First-born preterm	2.38	2.29-2.47	1.11	1.08-1.14	0.97	0.95-0.99	ref	1.08	1.06-1.11	1.18	1.14-1.22
First-born low birth weight	3.04	2.91-3.17	1.18	1.14-1.22	0.95	0.93-0.98	ref	1.18	1.14-1.21	1.30	1.24-1.35

Table 3A. Odds ratios of interpregnancy interval predicting adverse birth outcomes in fixed-effects sibling-comparison analyses

	Interpregnancy Interval (months)											
	0-5		6-11		12-23		24-35	36-71		72+		
Outcome Variable	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	OR	95% CI	
Preterm birth	1.17	1.07-1.28	1.08	1.01-1.15	0.99	0.93-1.05	ref	0.97	0.92-1.03	1.09	1.00-1.19	
Low birth weight	0.81	0.73-0.91	0.89	0.82-0.97	0.96	0.89-1.03	ref	1.04	0.96-1.12	1.29	1.16-1.44	
Small for gestational age	0.67	0.59-0.76	0.80	0.72-0.88	0.91	0.84-0.99	ref	0.98	0.90-1.07	1.39	1.24-1.57	

Table 3A presents sibling-comparison findings. Analyses were run comparing outcomes across the second- and third-born siblings and the dataset included 380,801 third-born siblings, there the analyses were restricted to these individuals and their sibling pair. Results from the cousin-comparison are supported; there is a small specific effect of short interpregnancy interval on odds of preterm birth that is further attenuated than the cousin-comparison. This attenuation is likely due to the increased control of unmeasured genetic and environmental factors. The relation between short interpregnancy interval and small for gestational age, and now also low birth weight, is slightly protective. And, links between long interpregnancy interval and all adverse birth outcomes are further attenuated, but still present.

Table 4A. Odds ratios of post-pregnancy interval and second-born adverse birth outcomes

	Interpregnancy Interval (months)											
	0-5		6-11		12-23		24-35	36-71		72+		
Outcome Variable	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	OR	95% CI	
Preterm birth	2.45	2.27-2.64	1.38	1.29-1.47	1.14	1.08-1.21	ref	1.07	1.01-1.13	1.07	1.00-1.13	
Low birth weight	2.80	2.57-3.05	1.41	1.30-1.52	1.11	1.03-1.19	ref	0.95	0.89-1.02	1.00	0.93-1.08	
Small for gestational age	2.06	1.86-2.29	1.24	1.13-1.35	1.06	0.98-1.15	ref	0.97	0.90-1.04	1.00	0.92-1.08	

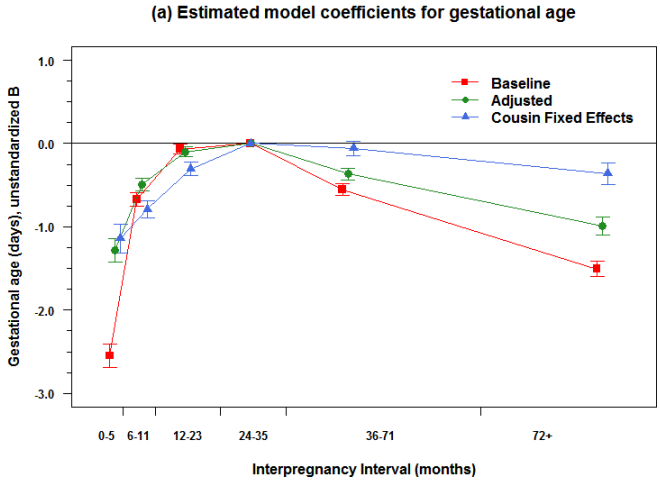
Analyses included the main sample of 1,084,777 second-born offspring with dummy coded post-pregnancy interval including if the family did not have a third-born child. As can be noted from Table 4A, the shortest post-pregnancy intervals are associated with increased risk for all adverse birth outcomes in the second-born offspring. This suggests that much of the effect specific to interpregnancy interval and increased risk for preterm birth is due to a familial factor that increases both the risk of short interpregnancy intervals as well as the risk for preterm birth. The lack of effect between long post-pregnancy interval and second-born adverse birth outcomes supports the main findings of a moderate specific effect of long interpregnancy interval and increased risk for adverse birth outcomes.

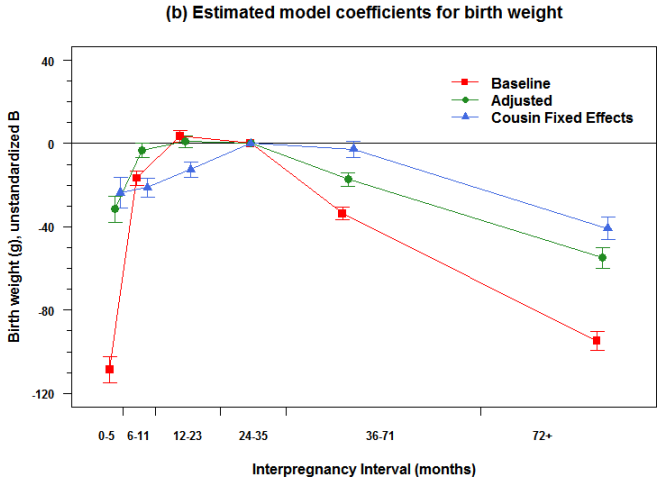
Table 5A. Odds ratios of interpregnancy interval predicting adverse birth outcomes across baseline, adjusted, and cousin-comparison models without adjusting for if the first-born was born preterm or low birth weight

Outcome Variable and Model	Interpregnancy Interval (months)										
	0-5		6-11		12-23		24-35	36-71		72+	
	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	OR	95% CI
Preterm birth											
Baseline	1.87	1.78-1.97	1.12	1.09-1.08	0.95	0.92-0.97	ref	1.24	1.20-1.28	1.77	1.70-1.83
Adjusted	1.54	1.46-1.62	1.08	1.04-1.12	0.95	0.93-0.98	ref	1.17	1.13-1.20	1.41	1.35-1.48
Cousin-comparison	1.28	1.19-1.38	1.10	1.04-1.16	0.98	0.94-1.03	ref	1.05	1.00-1.10	1.18	1.11-1.26
Low birth weight											
Baseline	1.73	1.62-1.85	1.03	0.98-1.08	0.92	0.89-0.95	ref	1.32	1.28-1.37	2.02	1.94-2.12
Adjusted	1.35	1.26-1.44	0.98	0.98-0.93	0.93	0.90-0.97	ref	1.21	1.17-1.26	1.50	1.42-1.58
Cousin-comparison	0.98	0.89-1.08	0.97	0.91-1.05	0.99	0.94-1.05	ref	1.11	1.05-1.18	1.41	1.31-1.53
Small for gestational age											
Baseline	1.33	1.23-1.43	0.88	0.83-0.92	0.90	0.86-0.93	ref	1.24	1.19-1.29	1.84	1.74-1.93
Adjusted	1.07	0.99-1.16	0.84	0.80-0.89	0.91	0.88-0.95	ref	1.13	1.09-1.18	1.41	1.32-1.49
Cousin-comparison	0.74	0.66-0.84	0.82	0.76-0.89	0.95	0.89-1.01	ref	1.00	0.93-1.07	1.37	1.26-1.50

Table 5A shows that conclusions from adjusted and cousin-comparison analyses that do not include the first-born's adverse birth outcomes (preterm birth and low birth weight) measures are the same as main analyses conclusions. These findings also suggest that the first-born's birth outcomes are predictive of the second-born's birth outcomes because adjusted estimates here are slightly elevated in comparison to the main models including the first-born's preterm birth and low birth weight indicators.

Figure 1A. Interpregnancy interval predicting continuously measured (a) gestational age, (b) birth weight, and (c) birth weight controlling for gestational age in baseline and cousin comparison analyses





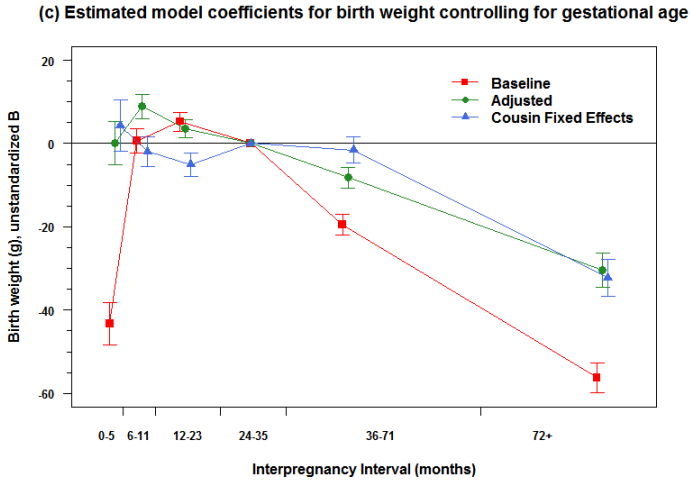


Figure 1A presents estimated coefficients (B) across baseline (red line, square points), adjusted (green line, circle points) and cousin-comparison fixed-effects models (blue line, triangle points) regression analyses. Echoing the findings from ordinal measurement and logistic models, Figure 1A shows that shorter interpregnancy intervals are associated with a decrease in gestational age, birth weight, and birth weight controlling for gestational age in the baseline models. This association only remains predictive in the cousin-comparison analyses for gestational age. The associations between long interpregnancy interval and all outcomes are robust across models.

2.6 A population-based quasi-experimental study of interpregnancy interval and offspring psychiatric and educational problems

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Abstract

Background: The interpretation of previously identified associations between short interpregnancy interval and increased risk for offspring psychiatric and educational problems is limited by unmeasured confounds.

Methods: Using population-based Swedish data registries, we estimated the independent association between interpregnancy interval and offspring psychiatric and educational problems while controlling for measured covariates and comparing differentially exposed cousins. Outcomes included autism spectrum disorder, attention-deficit hyperactive disorder, schizophrenia, substance use problems, suicide attempt and completion, and failing a grade. Sibling-comparisons and analyses with post-pregnancy interval also were used to test alternative hypotheses in sensitivity analyses.

Results: Although short (less than 12 months) interpregnancy interval was associated with each index of psychiatric and educational problem in the population and when controlling for measured covariates, the associations were all attenuated in the cousin-comparisons and sensitivity analyses. A robust association, albeit small in magnitude, between long interpregnancy interval (72 months or more) and attention-deficit hyperactive disorder was identified in cousin-comparisons (HR=1.16, 95% CI=1.01-1.34) and sensitivity analyses. Long interpregnancy interval was also found to robustly predict a decrease in offspring criminality (HR=0.89, 95% CI=0.84-0.94) and failing a grade (OR=0.92, 95% CI=0.86-0.97).

Conclusions: Previous research on short interpregnancy interval may have overestimated the associations with offspring psychiatric and educational problems. More research is needed to replicate the novel associations identified with long interpregnancy interval and to explore potential mechanisms.

Several recent studies have suggested that interpregnancy interval, or the duration between the birth of an earlier born child and the conception of the next child, is causally associated with major mental illness and academic achievement in child and adult populations [1-5]. For example, an interpregnancy interval of less than 6 months has been shown to increase the risk for offspring autism by 300% [2] and schizophrenia by 150% or more [1, 3]. A causal relation between interpregnancy interval and these burdensome outcomes is compelling because interpregnancy interval is a relatively modifiable risk factor [6]. Further, there are plausible causal mechanisms that could be responsible for the associations between short interpregnancy interval and these outcomes; a short interpregnancy interval may not allow for adequate restoration of the maternal nutritional foundation, especially of the fetal growth-relevant micronutrient folate [7, 8]. As such, the association could be influenced with a simple maternal folic acid supplement [9].

More research is needed before resources are directed at altering interpregnancy interval for targeted intervention/prevention efforts to reduce these outcomes. Traditional studies that compare outcomes across unrelated individuals that vary on interpregnancy interval may be confounded by genetic or environmental factors that influence both interpregnancy interval and the outcome [10]. Counfounding factors may include maternal socioeconomic variables, ethnicity, race, education, smoking status, and maternal age [11-17], for example. Additionally, within adolescent mothers, poor mental health, trauma history, and behavioral aggression correlate with shorter interpregnancy intervals [14, 18, 19]. Therefore, causal inferences from traditionally-designed studies [10] should be made with caution. Previous studies have also been limited by skewed measurement of interpregnancy interval (birth to birth rather than birth to

conception) [1, 5], which confounds spacing with gestational age, a factor that influences both interpregnancy interval [20] and the likelihood of offspring psychopathology [21].

Quasi-experimental designs that utilize design features, as well as statistical controls for covariates, are needed to test alternative explanations and rigorously examine whether causal inferences can be drawn from the associations identified in the entire population [22, 23]. For example, previous work has found that schizophrenia is predicted from both the index offspring's pre-pregnancy interval, as well as the post-pregnancy interval [1], suggesting the association is not due solely to the prior interval for the offspring. If familial confounding is responsible for the association, the pre-pregnancy interval would not confer a risk for schizophrenia unique from the post-pregnancy interval. A similar approach has also been used to predict self-harm, substance misuse, psychotic disorder, and affective disorder [5]. As others have pointed out, however, residual confounding and genetic factors that influence interpregnancy interval may still be driving the associations between both pre-pregnancy interval and post-pregnancy interval associations [24]. Other researchers have used instrumental variables that exploited the variation in birth spacing due to miscarriages when they investigated the impact of interpregnancy interval on educational achievement [25]. This approach, however, is also limited by unmeasured genetic and environmental confounds and results from "accidental" increases in interpregnancy interval due to miscarriage may not generalize to intentional manipulation of interpregnancy length.

In yet another quasi-experimental approach, one study examining interpregnancy interval and autism utilized a case-sibling control design wherein rates of autism were compared across first- and second-born offspring [2]. They found an association between short interpregnancy interval and odds of autism. Sibling-comparison designs rule out all unmeasured environmental

and genetic risks that make siblings similar [23, 26], which provides a rigorous alternative to traditional methods that compare unrelated individuals [27]. However, comparing outcomes between first- and second-born offspring when the risk in question is interpregnancy interval may be problematic in that the first-born offspring is not exposed to any interpregnancy interval length. Although the authors included a sensitivity analysis of the third-born offspring, the sample size was small [2]. Overall, although several quasi-experimental designs have been utilized to begin to pull apart confounding risk factors, converging evidence across design type, as well as replication, is needed, because each approach has unique limitations [26].

The current study uses one of the largest and most complete longitudinal, population-based databases in the world, the Swedish population registers, to examine the risk conferred by interpregnancy interval on several offspring psychiatric and educational problems. The specificity of associations between interpregnancy interval and outcome will be explored by including a broader range of disorders than has previously been tested. In particular, we included autism spectrum disorder (ASD), attention-deficit hyperactive disorder (ADHD), schizophrenia, substance use problems, suicide attempt and completion, and failing grades. To test for causal inferences, the current study utilized several designs, including the comparison of cousins. The cousin-comparison approach removes the possibility of birth order effects while accounting for unmeasured environmental or genetic factors that may be confounding the association between interpregnancy interval and each outcome. In an effort to further test alternative hypotheses, we also conducted sibling-comparison and a time-dependent comparison of risk following post-pregnancy interval in sensitivity analyses [1, 5].

Methods

Study population

After approval by the Institutional Review Boards at Indiana University and the Karolinska Institutet, data for the current study were obtained by linking information available in the following government-maintained, Swedish population-based registries: (1) the Medical Birth Registry provided data on more than 99% of pregnancies in Sweden since 1973 [28, 29]; (2) the Multi-Generation Register provided biological relationships for all individuals living in Sweden [30]; (3) the Migration Register provided information on dates for migration in or out of Sweden; (4) the Cause of Death Register provided information on dates and causes of all deaths; (5) the National Patient Registry provided diagnoses for all inpatient hospital admissions since 1973 and outpatient care since 2001 [31]; (6) the National Crime Register provided information on all criminal convictions since 1973 [32]; (7) the National School Register provided grades in all subjects for all students at the end of grade nine since 1983 [33]; (8) the Education Register provided information on highest level of completed formal education through 2008; and finally, (9) the longitudinal integration database for health insurance and social studies (LISA) provided yearly assessments of income, marital status, employment status, social welfare status, and education for all individuals 15 years or older since 1990 [34].

The initial sample included birth-related information for 3,403,185 individuals with valid maternal identifiers born between 1973 and 2008. We removed 74,666 multiple births and 25 individuals with missing parity and only the data for first-, second-, and third- born offspring in each maternal-based nuclear family were retained. We next used the Multi-Generation Register [30] to identify and drop 278,536 individuals whose mother who had at least one child born before 1973 as we did not have detailed birth information on individuals born prior to 1973. We then excluded 13,913 offspring with missing gestational age because this was needed to estimate

interpregnancy interval. Following the calculation of interpregnancy interval between the first- and second-born and the second- and third-born offspring in each family, we dropped 1,570,467 first-born offspring from the sample, as they did not have a preceding interpregnancy interval and were therefore not informative. The final cohort consisted of 1,465,578 second- and third-born offspring (i.e., 1,084,777 second-born and 380,801 third-born). The offspring were born to 1,100,045 distinct biological mothers and 1,108,165 distinct biological fathers. There were 797,038 distinct maternal-side grandmothers represented in the cohort used cousin-comparison models.

Measures

Interpregnancy interval

Interpregnancy interval was defined as the number of completed months between the birth of the first-born offspring and the date of conception of the second-born, index offspring. For use in sensitivity analyses, a parallel approach was used to calculate interpregnancy interval between the second- and third-born offspring on the subset of the population with 3 offspring per family. Interpregnancy intervals were categorized as 0 to 5 months, 6 to 11 months, 12 to 23 months, 24 to 35 months (referent), 36 to 71 months, and 72 or more months.

Offspring outcomes

We predicted ASD [35] indexed by International Classification of Disease (ICD) versions -9 and -10 diagnoses, including pervasive developmental disorder, and ADHD indexed by ICD-9 and -10 hyperkinetic disorder diagnoses [36]. For both ASD and ADHD, offspring had to have been at least 2 years old at the time of diagnosis. We also predicted criminality indexed by the age at first occurrence of any criminal conviction under the Swedish Penal code beginning at age 15, the Swedish age of legal responsibility [37, 38]; substance use problem defined as first

inpatient hospitalization involving a primary or secondary diagnosis of alcohol- or any other, non-nicotine, substance use disorder [39]; death by suicide as indicated by the cause of death record [40]; suicide attempt as indicated by the age at first attempt recorded in inpatient care records as the primary or secondary reason for care [40]; and severe mental illness as measured by the age at the first inpatient hospitalization for bipolar disorder, broadly defined schizophrenia, or other nonorganic psychotic disorders [41]. Except for criminality, the minimum age for all psychopathology outcomes was 12 years old. All clinical diagnoses were according to the year-dependent ICD- 8, -9, and -10 codes and are presented in the Appendix Table 1A. We also predicted failing grades as indexed by poor school performance in grade 9, commensurate with an average failing grade across 16 academic subjects [42].

Covariates

We included covariates that have been shown to vary with interpregnancy interval and correlate with psychopathological outcomes [21, 43]. Offspring sex, year of birth, maternal and paternal age at birth, maternal and paternal highest level of completed education, maternal and paternal nationality as Swedish or non-Swedish, whether the parents were cohabitating at the time of birth, and if the father of the second-born index offspring was the same as the father of the first-born offspring were all included in adjusted analyses. We also controlled for maternal and offspring-specific father criminality, substance use problem, death by suicide, suicide attempt, and severe mental illness. All parental psychopathology variables were defined the same as the offspring psychopathology outcomes, which are provided above with ICD codes listed in the Appendix Table 1A. The first-born being born preterm, defined as birth at <37 weeks of gestation, and the first-born being born low birth weight, defined as birth weight of <2500 g,

were also included as covariates in adjusted models. Dummy coding was used to handle missing covariate information.

Statistical analyses

We used Cox survival analyses for right-censored outcomes and logistic regression analyses for dichotomous outcomes (i.e., failing grades). For the survival analyses, if offspring had not received a diagnosis within the study period, they contributed person-time at risk until death, emigration, or the end date of follow-up (December 31, 2009), whichever came first.

A series of models were performed for each outcome. We first estimated the associations in the population in a baseline model only controlling for offspring sex (and birth year if the model was logistic). Next, we fit an adjusted model that controlled for all above mentioned offspring and parental covariates. The adjusted model was also performed on the entire sample of second-born offspring. The final, most rigorous, model was a fixed-effects cousin-comparison model that clustered at the grandmother level [44, 45] and included all above mentioned offspring-specific and parental covariates, as they may have varied between cousins. Therefore, the third model compared cousins with different interpregnancy interval lengths and thus accounted for all genetic and environmental factors shared among first-degree maternal cousins [23] as well as the influence of all covariates.

Sensitivity analyses

We ran sensitivity analyses to (1) test the assumptions and strength of findings from the cousin-comparison using a more rigorous sibling-comparison in a subsample of our population, and (2) explore if risk associated with interpregnancy interval is specific for the interval prior to the second-born offspring by utilizing the post-pregnancy interpregnancy interval (the interval

between the second- and third-born offspring) to predict the outcomes in the second-born offspring, similar to other studies [1, 5].

Results

Table 1 presents demographic information for the second-born offspring. Figure 1 panels (a) through (h) present point estimates [i.e., hazard ratios [(HR) or odds ratios (OR)] with 95% confidence intervals (CI) across offspring outcomes and model. In Figure 1, the baseline model is presented with a red line and square points, the adjusted model is presented with a green line and circle points, and the fixed-effect cousin-comparison analyses with a blue line and triangle points. Table 2 shows the parallel HR or OR with 95% CI estimates.

Short interpregnancy interval

In the baseline models an interpregnancy interval of 0-5 months was associated with increased likelihood of ADHD (HR=1.53, 95% CI=1.38-1.70) as compared with an interpregnancy interval of 24-35 months. The magnitude of association predicting ADHD was also elevated following an interpregnancy interval of 6-11 months (HR=1.38, 95% CI=1.29-1.48) and slightly elevated for an interval of 12-23 months (HR=1.12, 95% CI=1.06-1.18). Adjusting for measured covariates greatly attenuated the association between the shortest interpregnancy interval and ADHD (HR=1.19, 95% CI=1.07-1.32) and also slightly reduced the magnitudes for interpregnancy intervals of 6-11 months (HR=1.29, 95% CI=1.21-1.39). Fixed-effect cousin-comparisons eliminated the association for interpregnancy interval of 0-5 months and ADHD (HR=1.00, 95% CI=0.84-1.18), as well as for intervals of 6-11 months (HR=0.99, 95% CI=0.88-1.11) and 12-23 months (HR=0.94, 95% CI=0.85-1.04). As shown in Figure 1 and Table 2, this pattern of association was similar across all outcomes: short interpregnancy

intervals were related to the outcome in baseline analyses, the associations were attenuated in adjusted analyses, and magnitude was fully attenuated in fixed-effect cousin-comparisons.

Long interpregnancy interval

As compared with an interpregnancy interval of 24-35 months, longer interpregnancy intervals were associated with the outcomes in baseline analyses. The magnitudes of the associations were reduced in the adjusted models. The results in the cousin-comparisons were outcome-dependent. For example, when predicting ADHD in the baseline model, interpregnancy intervals of 36-71 months (HR=1.31, 95% CI=1.23-1.39) and 72 months or more (HR=2.35, 95% CI=2.19-2.53) were associated with increased risk. In adjusted models, the magnitudes of association were greatly reduced for 36-71 months (HR=1.08, 95% CI=1.01-1.14) and 72 months or more (HR=1.25, 95% CI=1.15-1.36). Fixed-effects cousin-comparisons further attenuated the association between ADHD and an interpregnancy interval of 36-71 months (HR=1.05, 95% CI=0.95-1.17) and 72 months or more, (HR=1.16, 95% CI=1.01-1.34), though the latter estimate was still statistically robust. For ASD, suicide attempt, severe mental illness, and substance use problem, the pattern of association was increased risk in baseline population analyses, attenuation in adjusted models, and full attenuation in fixed-effects cousin-comparisons, as presented in Figure 1 and Table 2.

For criminality and failing grade, although baseline and adjusted analyses showed increased risk for the outcomes following long interpregnancy interval, the fixed-effect analyses suggested a protective effect. For example, an interpregnancy interval of 72 months or more increased the risk for criminality in baseline analyses (HR=1.18, 95% CI=1.14-1.22). Adjusting for measured covariates greatly reduced the association (HR=1.04, 95% CI=1.01-1.08). Cousin

comparisons, however, showed that an interpregnancy interval of 72 months or more decreased the likelihood of criminality in the offspring (HR=0.89, 95% CI=0.84-0.94).

Sensitivity analyses

We performed a sibling-comparison on a subset of the sample (n=380,801 third born offspring plus their second-born sibling pairs) to test the assumptions and strength of findings from the cousin-comparison. This analysis compared the rates of outcome between the second- and third-born offspring if their interpregnancy interval categories differed. We found commensurate results; the risk from short interpregnancy interval was eliminated in sibling-comparisons across all outcomes, even ADHD. The risk following a long interpregnancy interval remained predictive for ADHD only (HR=1.43, 95% CI=1.18-1.74) and like the cousin-comparison findings, was associated with decreased risk for criminality (HR=0.80, 95% CI=0.74-0.85) and failing a grade (OR=0.77, 95% CI=0.71-0.83). Point estimates across all outcomes and interpregnancy interval categories for sibling-comparison analyses are presented in Appendix Table 2A.

We then explored if risk associated with interpregnancy interval is specific to the interval prior to the second-born offspring by utilizing the post-pregnancy interval (i.e., the interval between the second- and third-born offspring) to predict the outcomes in the second-born offspring. When controlling for the interpregnancy interval between the first- and second-born, as well as all measured covariates, we found that the shortest post-pregnancy interval was associated with increased risk for all the studied outcomes in the second-born. For example, a post-pregnancy interval of 0-5 months increased the risk for ADHD in the second-born (HR=1.38, 95% CI=1.18-1.63). This suggests that there is a familial component to the association, as the post-pregnancy interval cannot influence the second-born's birth outcome

because of the impossibility of reverse causation. Rather, the risk for short interpregnancy intervals may share a common factor with the studied outcomes. Elevated associations were also identified between the longest interpregnancy interval (i.e., more than 72 months) and the studied outcomes. These findings also support the idea that a general familial factor is partially influencing the associations between long interpregnancy interval and the outcomes. Point estimates across all outcomes and all post-pregnancy interval are presented in the Appendix Table 3A.

Discussion

Using Swedish population data, we explored the relation between interpregnancy interval and several measures of offspring psychiatric and educational problems, particularly problems associated with substantial morbidity and mortality. Although previous research has suggested an independent, and assumed causal, relation between shorter interpregnancy interval and increased risk for offspring educational problems, autism, schizophrenia, psychotic disorder, and self-harm [1-3, 5, 10], our findings suggest that previous conclusions may have overestimated these associations. All previous studies were limited because they were unable to control for unmeasured confounding factors. Notably, we found parallel conclusions for the associations between long interpregnancy interval and offspring psychiatric and educational problems; population-wide elevated associations were not robust when we compared differentially exposed cousins, except for a small association with ADHD. The analyses also suggested novel protective relations between an interpregnancy intervals of 72 months or more with criminality and a failing grade.

We were able to draw our conclusions by utilizing several designs that account for unmeasured confounds. The use of a family-based quasi-experimental design enabled us to account for unmeasured environmental and genetic factors that may influence the associations. The cousin-comparison approach also removed the difficulty of comparing outcomes across siblings where the first-born did not experience an interpregnancy interval [2, 10]. To test for alternative hypotheses and to examine the strength of our findings, however, we also included sibling-comparison and post-pregnancy interval analyses. Both sensitivity analyses provided commensurate results to our main cousin-comparison analyses in regards to the associations with short interpregnancy interval. In sibling-comparisons, short interpregnancy interval was not associated with any of the studied outcomes. The same conclusions were found in our post-pregnancy interval sensitivity analysis. In particular, we found that short post-pregnancy interval was associated for all outcomes, except substance use problem. This is in agreement with previous work showing increased risk for self-harm, substance misuse, and psychotic disorder [5]. These findings suggest that, rather than a specific effect of short interpregnancy interval on the studied outcomes, there are familial confounds that account for the associations. For example, there could be parental genetic, hormonal, or social factors that influence both the likelihood of a short interpregnancy interval and offspring psychiatric and educational problems.

In regards to long interpregnancy interval, sensitivity analysis results were also similar to the findings from the cousin-comparisons. In sibling-comparisons, the only outcome robustly associated with an increase risk following an interpregnancy interval of more than 72 months was ADHD, a finding that we identified in cousin-comparison analyses. The post-pregnancy interval analysis revealed that longer post-pregnancy intervals were associated with increased risk of ADHD. This elevation suggests that a portion of associations found in the population are

due to familial confounding. The decrease in magnitude from population analyses to sibling analysis (i.e., 2.35 baseline, 1.25 adjusted, 1.16 cousin, and 1.43 sibling) suggests that some familial confounding influences the relation, as magnitudes were greatly attenuated with increased control of measured and unmeasured confounds. Together these findings suggest an association between an interpregnancy interval of more than 72 months and offspring ADHD that is consistent with a causal inference. While more research is needed on potential mechanisms, it has been suggested that there is a gradual decline in reproductive capacity following a birth [46, 47]. This decline may impact the nutritional transfer during pregnancy thereby impacting fetal development. Future research would also benefit from exploring the role of breastfeeding in this complex association, as breastfeeding has been shown to elongate the interpregnancy interval but also further deplete maternal nutrient stores [39]. Alternatively, or perhaps in conjunction, infections may contribute to fertility issues, thereby lengthening the interpregnancy interval, as well as increasing risk for adverse offspring outcome [4, 6, 9, 46].

We also found that long interpregnancy interval was protective against criminality and failing a grade in sibling-comparison sensitivity analyses, similar to our cousin-comparison findings. Like the other post-pregnancy interval sensitivity analyses, findings suggested that some familial confounding was influencing the association. Increased parental resources due to the long spacing between births may specifically impacts these outcomes. Previous research on longer interpregnancy intervals have shown increased risk for adverse birth outcomes, such as preterm birth and low birth weight, [43] and these factors may decrease the likelihood of criminality and failing a grade [21, 48]. In general, however, research on the ramifications of long interpregnancy interval is limited. Some previous research grouped any interpregnancy interval over 36 [2, 10] or 45 months [1] together and treated the group as the reference category

thereby limited the conclusions that could be drawn. Others have simply combined any interpregnancy interval 37 months or longer [3], which may have distorted their conclusions regarding long interpregnancy interval. One study found that long interpregnancy intervals were associated with an increased risk for self-harm and substance misuse after adjusting for measured covariates was identified [5]. Our results did not support these findings, though our comparable outcomes of suicide attempt and substance use problem due to criminal conviction, were considerably different.

Our large, longitudinal dataset allowed us to study a large range of interpregnancy intervals, predict outcomes across childhood and adulthood, and utilize advanced designs based on family relatedness, several measured covariates, and timing to rigorously examine causal inferences. However, important limitations must also be considered. First, some outcomes were based on inpatient care; thus, we may be predicting the most severe cases of these disorders. Second, due to the relative ethnic homogeneity of the Swedish population, future research should perform quasi-experimental analyses across ethnic and racial groups because of interpregnancy intervals vary across these groups [13, 15, 16]. Similarly, prenatal care is advanced and comprehensive in Sweden and may have influenced interpregnancy interval length [49]. Thus, replication in different populations using different outcome measures is needed. Third, every design type we used has inherent limitations and assumptions [26]. To address these to our best ability, we drew conclusions from a combination of several statistical designs. Though some confidence intervals increased due to the reduced sample sizes of sensitivity analyses, we were able to more confidently state that associations apply across different family types (i.e., two child, three child, siblings and cousins). Thus, researchers will also need to use other designs. Fourth, we cannot rule out the possibility that “stoppage”, or the decision to not have a second

child due to diagnosis (e.g., ASD) in the first child, influenced family structure. If these families were not included in the sample because they did not have a second child, our estimates may be biased because of the non-inclusion of a subgroup with high familial risk for certain disorders. Finally, quasi-experimental designs are not randomized controlled studies; therefore, the design cannot rule out all possible confounding factors and causation cannot be proven [26, 27].

Overall, our findings suggest that previous magnitude of the independent or causal influence of short interpregnancy interval with increased risk for offspring psychiatric and educational problems were overestimated. Familial factors, either genetic or environmental, appear to influence both the likelihood of conceiving within a short period of time after giving birth, as well as the likelihood of numerous indexes of psychiatric and educational problems. We also identified a novel association between long interpregnancy interval and increased risk for ADHD, and decreased risk for criminality and failing a grade. Future researcher needs to explore the different mechanisms that may be driving these associations, such as biological preparedness for pregnancy, increased risk for infection, and increased parental resources.

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Table 1. Descriptive characteristics and covariates for the index, second-born offspring

Variable	Index Second-Born n (%)
n	1084777
Interpregnancy Interval (months)	
0-5	31882 (2.9)
6-11	133348 (12.3)
12-23	378088 (34.9)
24-35*	239506 (22.1)
36-71	2233574 (20.6)
72+	78379 (7.2)
Maternal Age (yrs)	
< 24	195838 (18.1)
25-29*	428614 (39.5)
30-34	337907 (31.2)
≥35	122418 (11.3)
Paternal Age (yrs)	
Missing	7501 (0.7)
< 24	73623 (6.8)
25-29*	329976 (30.4)
30-34	396776 (36.6)
≥35	276901 (25.5)
Maternal Highest Education	
Missing	5928 (0.6)
≤ 9 yrs	112816 (10.40)
1-3 yrs upper secondary*	529763 (48.8)
Post-secondary	436270 (40.22)
Paternal Highest Education	
Missing	13480 (1.2)
≤ 9 yrs	181987 (16.8)
1-3 yrs upper secondary*	539758 (49.8)
Post-secondary	349552 (32.2)
Maternal Swedish Nationality*	957697 (88.3)
Paternal Swedish Nationality*	950541 (87.6)
Missing	7501 (0.7)
Maternal Psychopathology	
Criminality	115630 (10.7)
Death by suicide	1065 (0.1)
Attempted suicide	24405 (2.3)
Substance use problem	18434 (1.7)
Severe mental illness	15554 (1.4)
Paternal Psychopathology	
Criminality	319930 (29.5)
Death by suicide	3357 (0.3)
Attempted suicide	16601 (1.5)
Substance use problem	33903 (3.1)
Severe mental illness	14268 (1.3)
Parents Not Cohabitating	85223 (7.9)
Missing	70040 (6.5)
First- and Second-born have Different Fathers	95015 (8.8)
Missing	17460 (1.6)

Table 2. Odds ratios of interpregnancy interval predicting second-born adverse birth outcomes across statistical models

Outcome Variable and Model	Interpregnancy Interval (months)										
	0-5		6-11		12-23		24-35	36-71		72+	
	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	OR	95% CI
ADHD											
Baseline	1.53	1.38-1.70	1.38	1.29-1.48	1.12	1.06-1.18	ref	1.31	1.23-1.39	2.35	2.19-2.53
Adjusted	1.19	1.07-1.32	1.29	1.21-1.39	1.13	1.07-1.19	ref	1.08	1.01-1.14	1.25	1.15-1.36
Cousin-comparison	1.00	0.84-1.18	0.99	0.88-1.11	0.94	0.85-1.04	ref	1.05	0.95-1.17	1.16	1.01-1.34
ASD											
Baseline	1.73	1.50-1.98	1.66	1.51-1.81	1.17	1.09-1.27	ref	1.26	1.16-1.37	2.12	2.00-2.44
Adjusted	1.59	1.38-1.84	1.64	1.50-1.79	1.20	1.11-1.30	ref	1.05	0.97-1.14	1.13	1.01-1.27
Cousin-comparison	1.11	0.87-1.42	1.12	0.96-1.31	0.93	0.81-1.06	ref	0.90	0.78-1.03	1.06	0.87-1.29
Criminality											
Baseline	1.57	1.51-1.63	1.22	1.19-1.25	1.04	1.02-1.06	ref	1.09	1.07-1.12	1.18	1.14-1.22
Adjusted	1.18	1.14-1.23	1.11	1.08-1.14	1.02	1.00-1.04	ref	1.04	1.06-1.06	1.04	1.01-1.08
Cousin-comparison	1.06	1.00-1.13	1.01	0.96-1.05	0.99	0.96-1.03	ref	0.98	0.95-1.02	0.89	0.84-0.94
Suicide attempt											
Baseline	1.57	1.41-1.75	1.31	1.22-1.41	1.00	0.95-1.07	ref	1.15	1.08-1.23	1.34	1.22-1.47
Adjusted	1.15	1.03-1.29	1.16	1.08-1.25	0.98	0.92-1.04	ref	1.06	0.99-1.13	1.04	0.94-1.15
Cousin-comparison	0.99	0.82-1.18	1.01	0.90-1.15	0.98	0.88-1.09	ref	1.10	0.99-1.23	0.88	0.75-1.04
Severe mental illness											
Baseline	1.48	1.28-1.73	1.48	1.34-1.63	1.20	1.11-1.29	ref	1.21	1.11-1.32	1.81	1.60-2.05
Adjusted	1.18	1.01-1.38	1.32	1.20-1.46	1.17	1.08-1.26	ref	1.10	1.01-1.20	1.31	1.14-1.50
Cousin-comparison	1.06	0.81-1.39	0.94	0.78-1.12	0.92	0.79-1.07	ref	1.01	0.86-1.18	1.02	0.80-1.31
Substance use problem											
Baseline	1.61	1.47-1.76	1.38	1.30-1.46	1.13	1.08-1.19	ref	1.20	1.14-1.27	1.62	1.51-1.74
Adjusted	1.17	1.07-1.28	1.23	1.15-1.30	1.11	1.05-1.16	ref	1.11	1.05-1.16	1.26	1.16-1.36
Cousin-comparison	1.03	0.90-1.19	1.07	0.97-1.18	1.04	0.96-1.13	ref	1.00	0.92-1.09	1.08	0.96-1.22
Failing grade											
Baseline	1.64	1.57-1.71	1.10	1.07-1.14	0.97	0.95-0.99	ref	1.22	1.19-1.25	1.45	1.40-1.49
Adjusted	1.06	1.01-1.11	0.97	0.94-1.00	0.95	0.93-0.97	ref	1.14	1.11-1.17	1.22	1.18-1.27

	Cousin-comparison	1.00	0.93-1.07	0.93	0.88-0.98	0.96	0.92-0.99	ref	1.01	0.97-1.06	0.92	0.86-0.97

Figure Legend.

Figure 1. Hazard and odd ratios across interpregnancy interval between the first- and second-born offspring predicting (a) attention-deficit hyperactive disorder (ADHD), (b) autism spectrum disorder (ASD), (c) criminality, (d) suicide attempt, (e) severe mental illness, (f) substance use problem, and (g) failing grade in baseline (red line and square points), adjusted (green line and circle points), and fixed-effect cousin-comparison analyses (blue line and triangle points). Reference interpregnancy interval ranged from 24-35 months.

Figure 1.

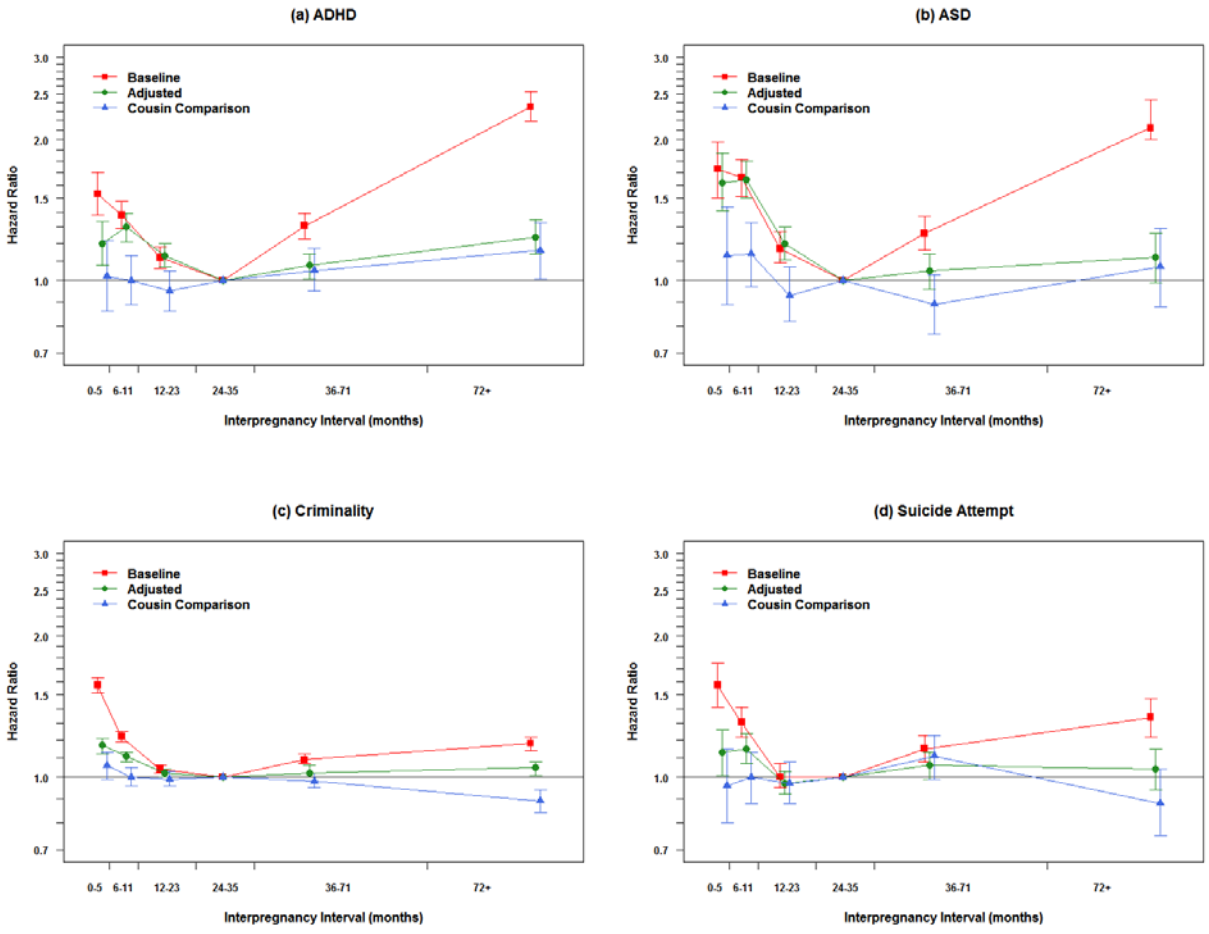
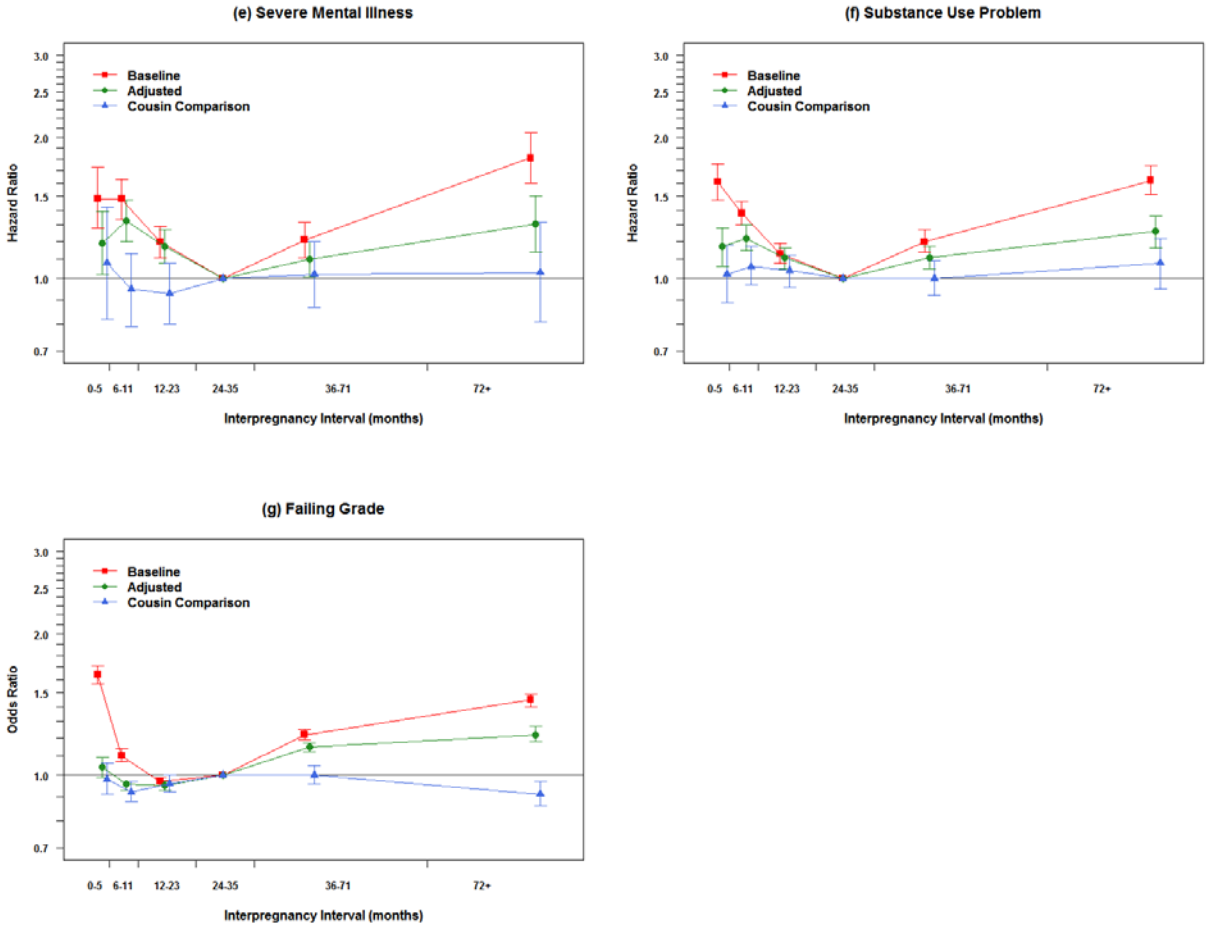

(a) ADHD
(b) ASD
(c) Criminality
(d) Suicide Attempt
Baseline
Adjusted
Cousin Comparison
Hazard Ratio
3.0
2.5
2.0
1.5
1.0
0.7
0-5
6-11
12-23
24-35
36-71
72+
Interpregnancy Interval (months)

Figure 1 cont.



Appendix: A population-based quasi-experimental study of interpregnancy interval and offspring psychiatric and educational problems

Table of Contents

Table 1A. International Classification of Disease (ICD) version and codes used to measure offspring and parental psychiatric problems

Outcome	Data Source	ICD Version	ICD Codes	Description
ADHD	NPR	9, 10	314, F90	Inpatient or outpatient primary diagnosis
ASD	NPR	9, 10	299, F84	Inpatient or outpatient primary diagnosis
Criminality	NCR	NA	NA	Earliest conviction for any criminal act
Death by suicide	COD	NA	NA	Certain and uncertain suicide as primary cause of death
Suicide attempt	NPR	8, 9, 10	E950-E959, E980-E989, X60-X84, Y870, Y10-Y34, Y872	Certain and uncertain attempts including violent, non-violent, and other
Substance use problem	NPR	8, 9, 10	303, 304, 305A, 305X, F10 (except x.5), F11-F19 (except x.5)	Alcohol or drug use (excludes nicotine) conviction
Severe mental illness	NPR	8, 9, 10	295, F20 296.1, 296.3, 296A-296E, 296W, F30-F31 291, 292, 296.0, 296.2, 296.9, 297-299, 296B, 296X, F32.3 x.5 in F10-F19	Inpatient or outpatient primary diagnosis of schizophrenia, bipolar disorder, or other non-organic psychoses

Note: ADHD = attention-deficit hyperactivity disorder, ASD = autism spectrum disorder, NCR = National crime register, COD = Cause of death register, NPR = Patient register, All except criminality have a minimum age of 12 while the minimum age for criminality is 15

Table 2A. Hazard and odds ratios of interpregnancy interval predicting psychiatric and educational problems in fixed-effects sibling-comparison analyses

	Interpregnancy Interval (months)										
	0-5		6-11		12-23		24-35	36-71		72+	
Outcome Variable	HR/OR	95% CI	HR/OR	95% CI	HR/OR	95% CI		HR/OR	95% CI	HR/OR	95% CI
ADHD	0.85	0.69-1.05	0.93	0.79-1.08	0.91	0.80-1.05	ref	1.01	0.87-1.17	1.43	1.18-1.74
ASD	0.83	0.63-1.10	0.88	0.73-1.07	0.82	0.69-0.98	ref	0.81	0.67-0.98	1.03	0.80-1.32
Criminality	1.02	0.95-1.10	1.00	0.95-1.06	0.99	0.95-1.04	ref	0.95	0.91-0.99	0.80	0.74-0.85
Suicide attempt	0.93	0.75-1.14	0.95	0.82-1.10	0.97	0.85-1.10	ref	1.17	1.02-1.34	0.82	0.68-1.00
Severe mental illness	0.89	0.66-1.19	0.81	0.66-1.01	0.88	0.73-1.06	ref	0.96	0.79-1.17	1.05	0.78-1.42
Substance use problem	0.99	0.85-1.16	1.06	0.95-1.19	1.02	0.92-1.12	ref	1.06	0.96-1.18	1.06	0.92-1.23
Failing grade	0.99	0.91-1.08	0.91	0.86-0.97	0.95	0.90-1.00	ref	0.95	0.90-1.00	0.77	0.71-0.83

Note: ADHD = attention-deficit hyperactive disorder, ASD = autism spectrum disorder

Table 2A presents sibling-comparison findings performed on a subsample consisting of 380,801 second- and third-born pairs. Results are commensurate with cousin-comparisons. Short interpregnancy intervals are not robustly predictive of any of the studied outcomes. Long interpregnancy interval is associated with an increased risk for ADHD and protective against criminality and failing a grade, all conclusions similarly found in cousin-comparisons.

Table 3A. Hazard and odds ratios of post-pregnancy interval and second-born psychiatric and educational problems

	Interpregnancy Interval (months)										
	0-5		6-11		12-23		24-35	36-71		72+	
Outcome Variable	HR/OR	95% CI	HR/OR	95% CI	HR/OR	95% CI		HR/OR	95% CI	HR/OR	95% CI
ADHD	1.38	1.18-1.63	1.24	1.10-1.39	1.20	1.09-1.33	ref	1.13	1.03-1.24	1.29	1.16-1.42
ASD	1.61	1.28-2.01	1.52	1.31-1.77	1.32	1.16-1.51	ref	1.01	0.88-1.15	1.12	0.97-1.30
Criminality	1.14	1.07-1.22	1.09	1.05-1.14	1.02	0.98-1.05	ref	1.04	1.01-1.08	1.19	1.15-1.23
Suicide attempt	1.12	0.93-1.34	1.14	1.00-1.29	0.97	0.88-1.08	ref	0.91	0.83-1.00	1.13	1.02-1.24
Severe mental illness	1.43	1.12-1.84	1.38	1.17-1.63	1.14	0.99-1.31	ref	0.94	0.83-1.07	1.10	0.96-1.26
Substance use problem	1.03	0.88-1.21	1.18	1.07-1.31	1.04	0.95-1.13	ref	1.03	0.96-1.11	1.22	1.12-1.32
Failing grade	1.22	1.13-1.32	1.12	1.07-1.18	1.06	1.02-1.11	ref	1.04	1.00-1.08	1.17	1.13-1.22

Note: ADHD = attention-deficit hyperactive disorder, ASD = autism spectrum disorder

Results presented in Table 3A were performed on the main sample of 1,084,777 second-born offspring with dummy coded post-pregnancy intervals including if the family did not have a third-born child. There were 380,801 informative third-born siblings in the sample. As can be noted from Table 3A, the shortest post-pregnancy intervals are associated with elevated magnitudes for all outcomes except substance use problem. This suggests that the associations found in population-wide analyses may be due to a confounding genetic or environmental familial factor, rather than a specific effect of short interpregnancy interval. This is because the timing of the post-pregnancy interval is not likely causally influencing the second-born's outcomes. A similar pattern can be noted in regards to long interpregnancy intervals. The effect found for ADHD, criminality, and failing grades, all outcomes that were found to be associated with long interpregnancy interval in cousin- and sibling-comparisons, may be understood as indicating that some of the association is due to confounding familial factors.

3. DISCUSSION

I used quasi-experimental designs to examine the causal inferences underlying the associations between early (i.e., preconception and pregnancy-related) risk factors and later physical, psychiatric, and educational problems across the six projects that form my dissertation. Using advanced quasi-experimental designs in the large and comprehensive Swedish population-based data registers allowed me to control a greater number of potential genetic and environmental confounds than has been previously achieved in human studies testing the Developmental Origins of Health and Disease (DOHaD) hypothesis.

In study 1, "Maternal stress and infant mortality: The importance of the preconception period", I utilized a natural experiment design that benefited from the random and specific timing of bereavement stress in the mother [1]. Study 2, "Offspring psychopathology following preconception, prenatal and postnatal maternal bereavement stress", also used the natural experiment design across preconception, prenatal, and postnatal periods but focused on longer-term psychiatric outcomes in the offspring [2]. Study 3, "Birth weight, physical morbidity, and mortality: A population-based sibling-comparison study" [3], used sibling-comparisons, as well as several sensitivity analyses, to directly examine the foundational associations of the DOHaD hypothesis, which was originally focused on low birth weight. In study 4, "Fetal growth and psychiatric and socioeconomic problems: A population-based sibling-comparison" [4], I extended my examination of birth weight to offspring psychiatric and socioeconomic outcomes. Study 5, "Interpregnancy interval predicting adverse birth outcomes", used a combination of cousin-comparisons, sibling-comparisons, and timing-dependent post-pregnancy intervals to examine associations between interpregnancy interval and adverse birth outcomes, as well as explore the parental, familial, and individual level correlates of the risk factor [5]. Finally, study

6, “A population-based quasi-experimental study of interpregnancy interval and offspring psychiatric and educational problems” tested previously proposed associations between interpregnancy interval and psychiatric and educational problems using a combination of several quasi-experimental designs [6].

3.1 Review of the Developmental Origins of Health and Disease (DOHaD) Hypothesis

The DOHaD hypothesis was established through research linking indices of fetal development (e.g., low birth weight) to adult physical disease (e.g., type 2 diabetes mellitus) [7]. The DOHaD hypothesis suggests that early life influences can causally impact later functioning because the insult is experienced during a sensitive developmental period [7]. Using the DOHaD framework, researchers have expanded on both the risk and outcomes studied. Ongoing research has identified key mediating mechanisms through which early risk factors influence subsequent problems, including epigenetic factors [8]. However, causal interpretations of the statistical associations is problematic at this point because most existing studies have been unable to rule out the possibility of environmental and genetic confounding [9, 10]. I set out to test the causal assumptions across several risks and outcomes that have been presented within the DOHaD framework.

3.2 Findings, Mechanisms, and Implications

3.2.1 Maternal stress

In study 1 we found an association between preconception maternal stress and increased risk for adverse birth outcomes and infant mortality [1]. This novel association is supported by previous intervention [11-13] and animal research [5]. We have also replicated the association

between preconception stress and infant mortality in a Danish population sample [4]. Interestingly, we did not find an association between prenatal maternal stress and infant mortality [1]. This counterintuitive finding has mechanistic implications. Maternal preconception stress may be translated to the future fetus by influencing nutritional, immunological, and/or hormonal maternal systems, [11-13] thereby affecting the mother's preparedness for pregnancy and the embryo during the vulnerable period of organogenesis [14, 15]. We did not identify a positive association between preconception stress and offspring psychopathology in study 2, however [2].

In study 2, we found that prenatal stress, in particular stress experienced during the third trimester, is associated with increased risk for offspring ASD and ADHD [2]. These results are in line with previous research [16-19]. The mechanisms underlying risk between prenatal stress and ASD and ADHD may include a disruption in stress-response systems [20, 21], prefrontal cortex development [22], gray matter density development [23], or confounding inherited factors that are associated both with the odds of bereavement stress exposure and offspring psychopathology [24]. The associations between adult psychiatric outcomes, such as schizophrenia and attempting suicide [2], however, were not found to be associated with prenatal stress exposure. Thus, previous research may have overestimated the associations between prenatal stress and psychiatric outcomes in adults [25-28].

In study 2, we also found novel associations between postnatal maternal bereavement stress and increased risk of ASD, ADHD, and suicide attempt in the offspring [2]. Postnatal developmental changes in the prefrontal cortex [29] or susceptibility to diminished parenting resources, sensitivity, and/or stimulation as a consequence of maternal stress [30, 31] may be particularly critical for ASD risk during the second postnatal year of development [32]. Postnatally, exposure to trauma, stress and maternal depression [30, 33] may adversely affect

offspring problem-solving abilities, cognitive ability, attachment, and/or compound genetic vulnerability to suicide [31, 34-36].

Across studies 1 and 2, our findings have several implications. The first is that quasi-experimental designs can be used to examine etiological mechanisms. By comparing risk across different developmental periods (i.e., preconception, prenatal, and postnatal periods), our findings were able to highlight the possibility that different mechanisms are responsible for the associations. The second implication is that the preconception period is an important period of development that should not be overlooked, especially for physical health outcomes and mortality. Third, continued research on the link between maternal stress exposure and neurodevelopmental disorders is needed. More specifically, trimester specific replication and trimester-relevant mechanisms need exploration. Finally, future research needs to explore these associations using different indicators of maternal stress and with a quasi-experimental fashion. Stress due to bereavement affects the survivor's psychological, cognitive, behavioral, endocrine, physiological-somatic, and immunological characteristics and can do so for months after the death [37]. Thus, bereavement stress, as measured in study 1 and 2 [1, 2], may act through a variety of mechanisms to influence offspring outcomes and future research needs to explore these possibilities. Other possible maternal stress indicators that are timing-specific and possibly available in a population–based data register include residential move, job loss, illness or major physical accident of a relative, and exposure to a natural disaster. Further, maternal stress as we measured it, may have been too minimal to be detected in the distal adult outcomes.

In summary, our findings on maternal stress are mixed and the associations are exposure-period and outcome-specific. Preconception stress appears to be tied with physical outcomes, while prenatal and postnatal stress are linked with childhood and adult neurodevelopmental

outcomes. Ties between prenatal maternal stress exposure and adult psychiatric outcomes were weaker than in previous studies and these associations should continue to be explored.

3.2.2 Offspring birth weight

Results from study 3, in which sibling-comparisons were used to examine the causal inferences of the associations between birth weight and physical health outcomes [3], support the foundational associations of the DOHaD hypothesis set forth by Barker [7]. Our findings suggests that causal inferences can be drawn, albeit with caution, between lower birth weight and increased risk for mortality after one year, cardiac-related death, hypertension, ischemic heart disease, pulmonary circulation problems, stroke, and type 2 diabetes mellitus. Further, risk for the studied outcomes increases continuously as birth weight decreases, even for those infants born within the normal (>2500g) range. While these associations have been assumed to be consistent with causal inferences, decades have passed without a rigorous examination of this assumption using quasi-experimental designs [2]. Perhaps knowing that low birth weight babies are at increased risk for these burdensome outcomes, may aide in diagnosis and early intervention efforts.

Epigenetic processes, including DNA methylation and histone modification, have been proposed as mechanisms underlying associations between low birth weight and physical outcomes [8, 38, 39]. Others have offered that non-genomic intergenerational inheritance may be at work [40]. Recent research has also suggested that important organs, such as the liver, may function at reduced capacity in lower birth weight individuals [3]. This difference can contribute to an increased load on other organs or lessen the effectiveness of certain medications [3], as compared with normal birth weight individuals. Another hypothesis is that if the ex utero

environment is mismatched from the conditions the fetus adapted to in utero, the phenotype established inside the womb may contribute to various diseases via metabolic set-point miss-adaptation [8, 39, 41]. For example, the combination of impaired fetal growth and rapid childhood weight gain is associated with increased risk for adult cardiovascular disease [39, 41-43]. Future research will need to explore these possible mediators in studies that can also rule out confounding factors.

We then utilized a sibling-comparison analysis, as well as several sensitivity analyses, to test the causal inferences between birth weight and psychiatric and socioeconomic problems in study 4 [4]. We found that lower birth weight independently predicted increased risk for ASD and ADHD even in sibling-comparison analyses. Though attenuated, associations were also robust when predicting psychotic or bipolar disorder and educational problems. Associations with suicide attempt, substance use problem, and social welfare receipt, however, were fully attenuated in sibling-comparisons. We showed a novel association between lower birth weight and decreased risk for criminality [4], similar to a previously identified inverse association between preterm birth and criminality [44]. Notably, the results were robust when we used other designs (e.g., cousin-comparison), which strengthened our conclusions.

Previous research has shown has shown that brain injury associated with low birth weight is associated with white matter abnormalities [45], which may be related to a vulnerability for neurodevelopmental disease. Other differences in brain development that correspond with neurodevelopmental problems, such as the amount of cortical surface area, brain volume, and caudate volume, have also been noted even across variations within normal birth weight [46]. Poor in utero nutrition may also be contributing to different fetal growth and altered brain development [47]. A mechanism that may underpin the protective effects between lower birth

weight and criminality, is that individuals that were born low birth weight may display personality characteristics linked with decreased risk-taking behaviors, receive increased parental monitoring, and/or form fewer relationships with delinquent peers. Future investigations into violent versus nonviolent crimes using advanced modeling may elucidate the association further [48].

Importantly, low birth weight is only a proxy for impaired fetal development [49]. Therefore, these results emphasize the need to closely examine the causes of low birth weight. Efforts should be made to improve on factors that influence low birth weight, such as decreasing maternal stress, decreasing smoking during pregnancy, and improving nutrition across both the preconception and prenatal periods. Future research may find that certain causes of low birth weight differentially predict increased risk for these studied outcomes, which may help to uncover differential etiological mechanisms across diseases.

3.2.3 Interpregnancy interval

We next examined the relation between interpregnancy interval, or the duration between the birth of an older sibling and the conception of the following offspring, on adverse birth [5], psychiatric, and educational problems [6] in studies 5 and 6 respectively. Cousin-comparison analyses, in addition to sibling-comparison and timing-dependent post-pregnancy interval sensitivity analyses, revealed that short interpregnancy intervals are not as strongly associated with adverse birth outcomes, psychiatric problems, or educational problems as previously suggested [50-54]. Only preterm birth was significantly increased following short interpregnancy intervals (i.e., less than 12 months) and the risk for ADHD was slightly elevated in magnitude. The mechanism that may be driving the independent association between short interpregnancy

interval and preterm birth may be a failure of contraction-related proteins to return to prepregnancy levels [55, 56], as one would assume nutritional depletion would affect birth weight and small for gestational age similarly. More research is needed to investigate the mechanism underlying the association with ADHD, though previous research has suggested that maternal nutritional depletion should be considered [52].

Long interpregnancy interval (e.g., 72 months or more), on the other hand, was associated with increased odds of preterm birth, low birth weight, small for gestational age, and ADHD [5, 6]. Where interpregnancy interval did not predict the studied outcome, confounding factors such as genetic, hormonal, environmental, or social factors that cousins or siblings share may help explain the statistical associations between long interpregnancy interval and offspring development. The only previously hypothesized causal mechanism linking long interpregnancy interval with increased risk for adverse outcomes is that there is a gradual decline in reproductive capacity following a birth [51, 57]; the longer the spacing, the greater the decline, perhaps impacting the nutritional transfer capacity during the next pregnancy and thus influencing fetal development. Infections may also contribute to fertility issues, thereby lengthening the interpregnancy interval, as well as increasing risk for adverse offspring outcome [57-60].

We also found that long interpregnancy interval length was protective against criminality and failing a grade. It may be that longer interpregnancy intervals allows for increased parental resources available for the later born, which decreases their likelihood of criminality or failing a grade. Interestingly, in study 5 we identified an increased risk for low birth weight following longer interpregnancy intervals [5] and in study 4, we showed that lower birth weight may be causally linked with a decreased risk for criminality [4]. Therefore, the association between

longer interpregnancy interval and reduced criminality, may be partially mediated by low birth weight and/or preterm birth [5, 44].

Across studies 5 and 6 we learned that associations between short interpregnancy interval and adverse birth outcomes, as well as offspring psychiatric and educational problems, may have been overestimated because previous studies may not have controlled for numerous confounds [5, 6]. In fact, in study 5 we found that interpregnancy interval is confounded with many maternal and paternal psychiatric, socioeconomic, and demographic factors [5]. Thus, quasi-experimental studies that can pull apart confounding genetic and environmental influences are necessary to test causal inferences when studying interpregnancy interval. The only associations with short interpregnancy interval that we noted as robust were predicting preterm birth and ADHD. Long interpregnancy interval, however, was robustly associated with increased risk for adverse birth outcomes and ADHD. Because some of our confidence intervals were large, these results need replication before intervention or prevention efforts are effected. Further, understanding the genetic and environmental factors that influence the variability in interpregnancy interval would help prevention and intervention efforts on the risk factor.

3.2.4 Summary across studies and future directions

The results of the existing family-based quasi-experimental studies provide mixed support for the DOHaD hypothesis, illustrating the critical need to use design features to rule out unmeasured environmental and genetic confounding when examining early risk factors [61, 62]. Our findings suggest that the links between early risk factors and psychiatric problems are strongest for neurodevelopmental disorders, such as ASD and ADHD. Positive associations between prenatal maternal stress, postnatal maternal stress, low birth weight, and to a lesser

extent, short and long interpregnancy interval, all support this conclusion [2, 4]. In addition, our findings suggest a strong association between perinatal risk and physical outcomes. Low birth weight increased the risk for cardiovascular disease, stroke, type II diabetes, and death after the first year of life, [3] while preconception stress increased the risk of infant mortality [1]. Interestingly a protective effect was identified across risk factors as well: low birth weight and long interpregnancy intervals were found to decrease the risk for criminality and failing a grade [4, 6].

The mechanisms driving the associations that are consistent with causal inference likely vary across the different preconception (e.g., stress and interpregnancy interval), prenatal (e.g., stress and low birth weight), and postnatal (e.g., stress) risk factors studied, as discussed in the previous sections. However, it is interesting that similar neurodevelopmental outcomes (i.e., ASD, ADHD, suicide attempt and completion) show elevated risk across all risk factors. This finding supports previous research showing a common genetic factor among these neurodevelopmental disorders [63, 64]. It may also indicate that the interrelatedness of these risk factors needed to be examined further, as interpregnancy interval, adverse birth outcomes, and maternal stress are correlated [50, 55, 65]. Furthermore, researchers have suggested that short pre- and post interpregnancy intervals may be indicative of increased maternal stress levels [66] and that it is the stress that impacts the offspring, not necessarily the interpregnancy interval. In the future, combining quasi-experimental design with detailed assessments of maternal condition and interpregnancy length would help clarify our findings [61].

We also did not find support for several previously reported associations [25, 52, 54], results that again support the continued use of quasi-experimental designs when studying the ramifications of early risk factors [61]. For example, cousin-comparison analyses did not support

associations between short interpregnancy interval and low birth weight, small for gestational age, and most childhood and adult psychiatric and educational problems. Our findings on interpregnancy interval suggest that environmental or genetic factors that are confounded with interpregnancy interval length [5] are driving these associations. Additionally, we did not find associations between prenatal maternal stress and adult psychiatric disorders [2], although we found independent associations with low birth weight [4]. This difference may indicate that factors other than stress that influence birth weight, such as nutrition or placental function, are responsible for the association between birth weight and adult psychiatric problems. Birth weight is indeed a proxy measure for impaired fetal development. Numerous factors can influence fetal development and result in low birth weight, [67] including maternal stress [39, 68, 69] and long interpregnancy interval [6, 50, 70-72]. These conclusions support continued examination into the mechanisms that lead to low birth weight, [67] which would guide subsequent translational research and intervention/prevention efforts.

Where our studies indicate that the risk is independently associated with the outcome, subsequent research needs to explore possible proximal mediating and moderating mechanisms [73]. Sibling- and cousin-comparisons help narrow the list of proximal mediators because the factors must (a) vary between siblings/cousins, (b) be correlated with the early risks within families, (c) be correlated with the outcome [74]. For example, we show that long interpregnancy interval [6] and low birth weight [4] are associated with increased risk for ADHD, yet these risk factors are also related to each other [5]. Other potential mediators include maternal infection and preeclampsia [75]. If the data were available, examining placental functioning would also be highly interesting and likely informative because of the important role of the placenta in fetal development and translating the maternal condition to the fetus [76-78]. Combining these

multiple levels of risk factors will be important in understanding the mechanisms driving associations consistent with causal inferences.

An important next step also includes examining the role of fathers, an often over-looked contributor to early development. More specifically, future research should examine the degree to which confounding is due to paternal influence [79]. Comparing the ramifications of an insult to the father versus mother would begin to clarify the possible role of paternal confounding [80]. For example, the ramifications of paternal bereavement stress across the offspring's preconception and prenatal periods could be compared with our study 1 and 2 outcomes [1, 2]. If the associations are truly due to maternal preparedness or offspring intrauterine exposure, then maternal exposure to an insult would have a greater influence than paternal exposure. It will also be important to characterize fathers who bear children after short and long interpregnancy, as paternal affects may be large contributors to the associations between interpregnancy interval and offspring outcomes.

Finally, as discussed above, future research needs to continue to explore the role of the preconception period. The robust [1] and replicated [4] findings of increased risk for infant mortality after preconception maternal stress deserves attention. Exploring if the association exists across different types of stressors, if other risk factors, such as poor maternal nutrition or infection, are associated with the same outcomes, and what factors promote resilience may be fruitful lines of future research.

3.2 Strengths

The Swedish population registers enabled me to conduct the current studies. This large combination of several datasets is unparalleled in size and scope. The data are prospectively

collected, longitudinal, and genetically-informed, which made it possible to utilize advanced quasi-experimental designs. In addition, the risk factors and outcomes we studied were well validated and clinically interpretable [6, 81-88].

The variety of quasi-experimental designs used across our analyses partially addresses the weaknesses inherent in traditional epidemiological studies that only included one child per family by reducing potential threats to internal validity by controlling for unmeasured confounds [61, 89, 90]. By using a natural experiment design when examining perinatal maternal stress, we were able to draw stronger conclusions while testing for sensitive periods within the preconception, prenatal, and postnatal periods [91]. By using cousin-comparisons and sibling-comparisons, we were able to control family factors, both genetic and environmental, that could increase the risk of experiencing both the risk and the outcome [74]. In addition to controlling for familial confounds, we also statistically controlled for numerous measured covariates that may have varied within the related dyad, thereby further strengthening the internal validity of the findings. Using various sensitivity analyses we were able to address other limitations, including the Stable Unit Treatment Value Assumption and the assumption that findings from cousin- and sibling-comparisons generalize to individuals that do not have these family relationships [74, 92-94].

3.3 Limitations

Despite the strengths of our dataset and analyses, there are limitations to both of these aspects. For example, the use of secondary data limited our selection of outcomes. More specifically, our outcomes were limited to data recorded in hospitals, on conviction records, or as part of a census tracking. The use of inpatient records and criminal convictions may be capturing

the most severe population; therefore, results may not generalize to all populations. Further, use of inpatient records or psychiatric outcomes may not capture date of disease onset, and this may have influenced the associations. Examining the association between early risk factors and outpatient hospitalization records, clinic diagnoses, symptom counts, and self or other reports is important to examine the specificity of findings and should be performed in future research. Future studies will also need to address the external validity of our findings because the high quality of prenatal care and relative racial homogeneity of the Swedish population may make the generalizability of our findings to other countries and cultures difficult.

Importantly, natural experiments, cousin-comparisons, and sibling-comparisons are not randomized controlled studies. Therefore, the designs cannot rule out all possible confounding factors; we cannot definitively draw true causal conclusions. For example, there still may be unmeasured variables that differ between siblings that causally influence the outcome [95, 96]. Additionally, when the risk factors are not associated with the outcomes, cousin- and sibling-comparisons cannot determine the source of confounding [74, 93]. Statistical power also becomes an issue when using cousin- and sibling-comparison analyses to examine associations between rare risks and rare outcomes, such as stress during a particular trimester and schizophrenia. Thus, the confidence intervals around some of our associations are large. These limitations suggest future research in these areas is particularly crucial.

3.4 Future Directions for Studying the Developmental Origins of Health and Disease Hypothesis

This set of studies motivates several overarching directions for future studies. First, quasi-experimental research that utilizes a variety of designs is necessary [61, 62]. Combining designs and generating new creative approaches will help researchers address inherent

limitations in each design and will advance our understanding of developmental psychopathology. Second, research should aim to address questions from multiple levels of analysis. Due to the sample size requirements of most quasi-experimental designs, studies on early risk factors usually do not use detailed risk or outcome assessments. Therefore, future studies on early risk factors will need to resourcefully combine prospectively collected, in-depth observational and self-report data with quasi-experimental designs to clearly understand the associations identified using large population data [61, 97].

Third, especially for the associations that we have identified as consistent with a causal inference, more research on potential mediating mechanisms needs to be conducted. We hope that our findings will generate questions in researchers investigating developmental mechanisms. And in turn, if advances are made in identifying mechanisms, we aim to examine the role of proxies of those mechanisms within our large dataset using advanced statistical designs. Examining the role of maternal immunological and placental functioning are particularly exciting possibilities [59, 75, 77]. More proximal mediating risk factors, such as those that occur during other sensitive periods of development like adolescence, can also be explored. In this way, a life-span perspective on risk and outcome could be taken which might provide a more complete picture of how early risk factors cascade into adult problems. Fourth, the DOHaD framework and quasi-experimental designs can also be used to study the causal inferences between reportedly beneficial (and reportedly causal) early factors (e.g., breastfeeding) and positive outcomes [98]. Future studies focusing on healthy outcomes have the potential to provide not only information about the causal factors that promote positive outcomes, but also to inform the field about what factors may reduce the negative impact of early risk factors.

3.5 Conclusions

Our findings have established novel associations, supported previous conclusions, and refuted previous associations that were assumed to be causal. Our studies benefitted from the combination of several quasi-experimental designs and an unmatched dataset. Our findings are reason to continue to pursue quasi-experimental approaches. We found that preconception stress was an important risk factor that deserves future examination. We supported the conclusion that low birth weight is causally associated with adult physical health problems and several psychiatric problems. We also found that associations between short interpregnancy interval and psychiatric problems may not be causal, as previously assumed. Long interpregnancy interval, however, appears may be causally related to increased risk for adverse birth outcomes and ADHD. Overall, our findings emphasize that the DOHaD hypothesis is a useful framework for examining developmental psychopathology. Causal inferences, however, should be considered, and tested, on a risk factor-by-outcome basis.

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95. D'Onofrio, B.M., et al., *The role of children of twins designs in elucidating causal relations between parent characteristics and child outcomes.* Journal of Child Psychology and Psychiatry, 2003. **44**(8): p. 1130-1144.

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QUETZAL A. CLASS

CURRICULUM VITAE

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EDUCATION

2014-present Indiana University (IU) School of Medicine - Indianapolis, IN
APA-Accredited Predoctoral Clinical Internship

2007-2015 IU - Bloomington, IN
Department of Psychological and Brain Science
APA-Accredited Clinical Science Program
Ph.D. in Clinical Science
Dissertation: Testing Causal Hypotheses and Associations between Perinatal Risk Factors and Offspring Morbidity and Mortality
Defended: June 2014
Advisor: Brian M. D'Onofrio, Ph.D.

2001-2005 University of California, San Diego (UCSD) - La Jolla, CA
Bachelor of Sciences with Highest Honors in Psychology
Graduated Magna Cum Laude
Honors Title: Affective valence, stimulus attributes, and P300: Normal vs. scrambled images
Honors Advisor: John Polich, Ph.D.

FUNDING

2013-2014 IU College of Arts and Sciences Dissertation Year Research Fellowship
Mabel LaDuke Lauder Fund recipient

2011-2013 National Institute of Mental Health (MH094011)
Kirschstein National Research Service Award (NRSA)
Individual Pre-doctoral Fellowship, 2nd percentile
Title: "Early Stress and Suicidal Behavior"

2009-2011 National Institute of Health (5TL1RR025759-02)
Indiana Clinical and Translational Sciences Institute (CTSI)
Individual Career Development Award

2007-2009 National Institute of Child Health and Human Development (HD07475)
Institutional Research Training Grant in Developmental Process

2004 UCSD Chancellor's Research Scholarship
Competitive $3,000 scholarship supporting undergraduate honors research project

HONORS AND AWARDS

2014 Society for a Science of Clinical Psychology (SSCP) Outstanding Student Researcher Award
Nation-wide, faculty nominated competitive award for exemplary research contributions to the science of clinical psychology and for future promise as a rising star in the field of clinical science.

2014 Indiana Psychological Association 1st Place Student Abstract Competition Award
Recognition and monetary award based on quality and importance gleaned from abstract of poster submission to fall conference, all student levels considered

2013 J.R. Kantor Outstanding Graduate Student Research Award, Department of Psychological and Brain Sciences, IU
Faculty-nominated award to graduate student for research promise in the field of psychology

2012 IU Graduate School, Graduate and Professional Student Organization, Travel Grant
Competitive award supporting presentation at Society for Gynecological Investigation annual meeting, San Diego, CA

2010 Most Outstanding Associate Instructor for Methods of Experimental Psychology, Department of Psychological and Brain Sciences, IU
Based on student ratings and faculty evaluation for creative approach to the course

2010 IU Office of the Vice President of International Affairs Pre-Dissertation Travel Grant
Funded extended research and training at the Karolinska Institutet, Stockholm, Sweden

2010 Behavioral Genetics Association Annual Conference, Travel Grant
Competitive award supporting travel and presentation at conference

2009 Early Life Programming and Neurodevelopmental Disorders Conference, Travel Grant
Competitive award to support all funds needed to attend and present at invite-only conference

2005 UCSD Honors with Highest Distinction in the Major of Psychology
Awarded for graduating with psychology major GPA of 4.0

2001-2005 UCSD Provost's Honor Awards
Awarded for maintaining a GPA of 3.5 or higher with 12 or more graded units per quarter

2004 UCSD Psi Chi Psychology Honor Society Inductee
Membership based on maintaining a GPA of 3.0 or higher as a psychology major

2003 UCSD Opportunities Abroad Scholarship
Competitive merit-based award to support study abroad

2003 Irvine Memorial Scholarship
Award based on academic merit and financial need to support undergraduate education

2002 William H. Stout Scholarship
Award based on academic merit to support undergraduate education

PUBLICATIONS

PEER-REVIEWED

1. **Class, Q.A.,** Mortensen, P.B., Henriksen, T.B., Dalman, C., D'Onofrio, B. M., & Khashan, A. S. (in press). Preconception maternal bereavement and infant and childhood mortality: A Danish population-based study, *Psychosomatic Medicine.*
2. Sujan, A.C., **Class, Q.A.**, Coyne, C.A., Rickert, M.E., Oberg, A.S., Larsson, H., Almqvist, C., Lichtenstein, P., & D'Onofrio, B.M., (in press). A genetically informed study of the associations between maternal age at childbearing and adverse perinatal outcomes, *Behavior Genetics*.
3. D'Onofrio, B.M., **Class, Q.A.**, Sujan, A.C., Rickert, M.E., Larsson, H., Oberg, A.S., Sjölander, A., Almqvist, C., & Lichtenstein, P. Translational epidemiologic approaches to understanding the consequences of early exposures, *Behavior Genetics*.
4. **Class, Q.A.,** Rickert, M.E., Larsson, H., Lichtenstein, P., & D'Onofrio, B.M., (2014). Fetal growth and psychiatric and socioeconomic problems: A quasi-experimental population-based study, *British Journal of Psychiatry, 205,* 355-361.
5. **Class, Q.A.,** Abel, K.M., Khashan, A.S., Rickert, M.E., Dalman, C., Larsson, H., Hultman, C.M., Långström, N., Lichtenstein, P., & D'Onofrio, B.M. (2014). Offspring psychopathology following preconception, prenatal, and postnatal maternal bereavement stress, *Psychological Medicine, 44(1),* 71-84.
6. **Class, Q.A.,** Rickert, M., Lichtenstein, P., & D'Onofrio, B.M., (2014). Birth weight, physical morbidity, and mortality: A population-based sibling-comparison study, *American Journal of Epidemiology, 179*(5), 550-558.
7. D'Onofrio, B.M., **Class, Q.A.**, Lahey, B. & Larsson, H. (2014). Testing the developmental origins of health and disease hypothesis for psychopathology using family-based quasi-experimental designs, *Child Development Perspectives, 8,* 151-157.
8. McCoy, B.M., Rickert, M.E., **Class, Q.A.**, Larsson, H., Lichtenstein, P., D'Onofrio, B.M. (2014). Mediators of the association between parental severe mental illness and offspring neurodevelopmental problems, *Annals of Epidemiology, 24,* 629-634.
9. **Class, Q.A.,** Khashan, A.S., Lichtenstein, P., Långström, N., & D'Onofrio, B.M. (2013). Maternal stress and infant mortality: the importance of the preconception period, *Psychological Science, 24 (7),* 1309-1316.
10. **Class, Q.A.,** Verhulst, J., & Heiman, J. (2013). Postpartum "depression": Exploring the heterogeneity of clinical presentation and functional impairment, *Journal of Reproductive and Infant Psychology, 31 (2),* 183-194.
11. D'Onofrio, B.M., **Class, Q.A.,** Rickert, M.E., Larsson, H., Långström, N., Lichtenstein, P. (2013). Preterm birth and mortality and morbidity: A quasi-experimental study, *JAMA Psychiatry, 70,* 1231-1240.
12. **Class, Q.A.**, D'Onofrio, B.M., Singh, A.L., Ganiban, J., Spotts, E., Lichtenstein, P., Reiss, D., & Neiderhiser, J. (2012). Current parental depression and offspring perceived self-competence: a quasi-experimental examination, *Behavior Genetics, 42 (5),* 787-797.

13. **Class, Q.A.,** Lichtenstein, P., Långström, N., & D'Onofrio, B.M. (2011) Timing of prenatal maternal exposure to severe life events and adverse pregnancy outcomes: A population study of 2.6 million pregnancies. *Psychosomatic Medicine, 73,* 234-241.
14. Buss, C., Davis, E.P., **Class, Q.A.**, Gierczak, M., Pattillo, C., Glynn, L. & Sandman, C.A. (2009). Maturation of the human fetal startle response: Evidence for sex-specific maturation of the human fetus. *Early Human Development, 85*, 633-638.
15. Cano, M.E., **Class, Q.A.**, & Polich, J. (2009). Affective valence, stimulus attributes, and P300: Color vs. black/white and normal vs. scrambled images. *International Journal of Psychophysiology, 71 (1),* 17-24.
16. **Class, Q.A.**, Buss, C., Davis, E.P., Gierczak, M., Pattillo, C. & Sandman, C.A. (2008). Low levels of corticotropin-releasing hormone during early pregnancy are associated with precocious maturation of the human fetus. *Developmental Neuroscience, 30,* 419-426.
17. Buss, C., **Class, Q.A.**, Tan, E.T., Gierczak, M., Patillo, C., Davis, E.P., & Sandman, C.A. (2007). Fetal heart rate responses over pregnancy predict infant mental and motor development during the first year of life. *Early Human Development, 83,* S114-S115.

BOOK CHAPTERS

18. Sandman, C.A., **Class, Q.A.,** Glynn, L. and Davis, E.P. Neurobehavioral disorders and DOHaD. In C. Rosenfeld (Ed.), *The Epigenome and Developmental Origins of Health and Disease,* Academic Press/Elsevier, Waltham, MA, 2015.

MANUSCRIPTS UNDER REVIEW

19. Heiman, J., **Class, Q.A.,** Cheng, H., Rupp, H.A., Sengelaub, D.R., & Ketterson, E.D. (under review). Amygdala, whole brain and subjective responses to negative images in depressed vs. nondepressed postpartum women and intranasal oxytocin.
20. **Class, Q.A.,** Rickert, M.E., Oberg, A.S., Larsson, H., Lichtenstein, P., & D'Onofrio, B.M., (under review). Interpregnancy interval predicting adverse birth outcomes: A population-based quasi-experimental study
21. **Class, Q.A.,** Rickert, M.E., Larsson, H., Oberg, A.S., Lichtenstein, P., & D'Onofrio, B.M., (under review). A population-based quasi-experimental study of interpregnancy interval and offspring psychiatric and educational problems
22. Bramson, L.M., Rickert, M.E., **Class, Q.A.**, Sariaslan, A., Larsson, H., Lichtenstein, P., & D'Onofrio, B.M. (under review). The association between childhood relocations and subsequent risk of suicide attempt, psychiatric problems, and low academic achievement.

MANUSCRIPTS IN PREPARATION

23. **Class, Q.A.,** Rickert, M.E., Oberg, A.S., Larsson, H., Lichtenstein, P., & D'Onofrio, B.M., (in preparation). Using family-based quasi-experimental approaches to examine the association between prenatal maternal infection and adverse offspring outcomes.

PRESENTATIONS

INVITED

1. **Class, Q.A.,** Rickert, M., Larsson, H., Lichtenstein, P., & D'Onofrio, B.M., (August, 2013). Using sibling comparisons to examine the long-term ramifications of low birth weight, Paper presented at Chapman University, Orange, CA.
2. **Class, Q. A.,** Chan, T., & Bates, J. (June, 2012). Parent Behavior Training, Workshop presented at Circles Initiative Meeting, South Central Community Action Program, Monroe County, Bloomington, IN.
3. **Class, Q. A.,** Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (May, 2011). Consequences of
   Prenatal Maternal Stress: Testing Causal Assumptions in Humans, Paper presented at the National Pre-doctoral Clinical Research Training Program Meeting, St. Louis, MO.
4. **Class, Q. A.,** Ahn, W.Y., Coyne, C.A., Donahue, K., Endres, M., Erickson, M., Goodnight, J., & Bates, J. (April, 2009). Parent Behavior Training: Clinical applications, Workshop presented at Indiana University, Psychological and Brain Sciences Clinical Colloquium, Bloomington, IN.
5. **Class, Q. A.,** Ahn, W.Y., Coyne, C.A., Donahue, K., Endres, M., Erickson, M., Goodnight, J., & Bates, J. (April, 2009). Parent Behavior Training: Addressing resistance, Workshop presented at Healthy Families Monroe, Bloomington, IN.
6. **Class, Q. A.,** D'Onofrio, B. M., Langstrom, N., & Lichtenstein, P. (July, 2009). Timing of prenatal maternal stress, Paper presented at the meeting for Early Life Programming and Neurodevelopmental Disorders, Philadelphia, PA.

CONFERENCE

7. D'Onofrio, B.M., Oberg, A.S., **Class, Q.A.**, Rickert, M.E., Bramson, L.M., Almqvist, C., Larsson, H., & Lichtenstein, P. (June, 2015). Maternal body mass index and offspring fetal growth: A cousin- and sibling-comparison study, Paper presented at the Annual Behavior Genetics Conference, San Diego, CA.
8. **Class, Q.A.**, Oberg, A.S., Rickert, M.E., Larsson, H., Lichtenstein, P., & D'Onofrio, B.M., (March, 2015). A population-based quasi-experimental study of interpregnancy interval and offspring neuropsychiatric and academic outcomes, Poster presented at the Society for Research in Child Development Biennial Meeting, Philadelphia, PA.
9. Bramson, L., Rickert, M.E., **Class, Q.A.**, Sariaslan, A., Larsson, H., Lichtenstein, P., & D'Onofrio, B.M. (March, 2015). The association between childhood relocations and risk of suicide attempt, psychiatric problems, and low academic achievement, Poster presented at the Society for Research in Child Development Biennial Meeting, Philadelphia, PA.
10. D'Onofrio, B., Oberg, A.S., **Class, Q.A.**, Rickert, M.E., Bramson, L., Almqvist, C., Larsson, H., & Lichtenstein, P. (March, 2015). Maternal Body Mass Index, Adverse Birth Outcomes, and Infant Mortality: A Cousin- and Sibling-Comparison Study, Paper presented at the Society for Research in Child Development Biennial Meeting, Philadelphia, PA.
11. **Class, Q.A.,** Rickert, M.E., Larsson, H., Oberg, A.S., Lichtenstein, P., & D'Onofrio, B.M., (November, 2014). A population-based quasi-experimental study of

interpregnancy interval and offspring neuropsychiatric and academic outcomes, Poster presented at the Annual Indiana Psychological Association Fall Conference, Indianapolis, IN.

12. **Class, Q.A.,** Mortensen, P.B., Pedersen, M.G., Henriksen, T.B., Dalman, C., D'Onofrio, B. M., & Khashan, A. S., (November, 2013). Preconception maternal exposure to bereavement stress increases the risk of infant and childhood death: a Danish population-based study, Paper presented at the Developmental Origins of Health and Disease Annual World Congress, Singapore.
13. D'Onofrio, B., Rickert, M., **Class, Q.A.,** Kuja-Halkola, R., Larsson, H., Lichtenstein, P. (April 2013). Paternal age at childbearing and offspring risk for autism: A population-based quasi-experimental study, Paper presented at the Society for Research in Child Development Biennial Meeting, Seattle, WA.
14. **Class, Q. A.,** Khashan, A., Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (March, 2012). Pregestational and prenatal maternal stress exposure predicting risk for infant mortality, Poster presented at the Society for Gynecological Investigation annual meeting, San Diego, CA.
15. **Class, Q. A.,** Khashan, A., Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (March, 2012). Pregestational and prenatal stress predicting infant mortality, Poster presented at the Women in Science Research Conference, Bloomington, IN.
16. D'Onofrio, B.M., Rickert, M., **Class, Q.A.,** Langstrom, N., Lichtenstein, P., (September, 2011). Rigorously testing the fetal programming hypothesis, Paper presented at Indiana University, Psychological and Brain Sciences Developmental Seminar, Bloomington, IN.
17. **Class, Q. A.,** Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (June, 2011). Risk for suicidal behavior after early maternal stress exposure, Paper presented at the Behavioral Genetics Association annual meeting, Newport, RI.
18. **Class, Q. A.,** Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (April, 2011). Prenatal maternal stress and adverse birth outcome: Using siblings to test causality, Poster presented at the Indiana Clinical and Translational Sciences Institute Annual Meeting, Indianapolis, IN.
19. **Class, Q. A.,** Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (April, 2011). Quasi-experimental investigation of prenatal maternal stress and adverse birth outcomes: A population study, Poster presented at the Society for Research in Child Development Biennial Meeting, Montreal, Quebec, Canada.
20. **Class, Q. A.,** Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (November, 2010). Prenatal maternal stress: Consequences from Birth to Death, Paper presented at the Psychological and Brain Sciences Clinical Science Seminar, Bloomington, IN.
21. **Class, Q. A.,** Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (October, 2010). Timing of prenatal maternal stress and adverse pregnancy outcomes, Poster presented at the Indiana Clinical and Translational Sciences Institute Indiana Retreat, Bloomington, IN.
22. Buss, C., Davis, E. P., **Class, Q. A.,** Gierczak, M., Patillo, C., Glynn, L. & Sandman, C. A. (July, 2010). Fetal heart rate responses over pregnancy predict infant mental and motor development during the first year of life, Poster presented at the World Association for Infant Mental Health, Leipzig, Germany.

23. **Class, Q. A.,** Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (April, 2010). Investigating the relation between human prenatal stress and adverse pregnancy outcomes: A population study of 2.6 million pregnancies, Poster presented at the Indiana Clinical and Translational Sciences Institute Annual Meeting, Indianapolis, IN.
24. **Class, Q. A.,** Lichtenstein, P., Langstrom, N., & D'Onofrio, B. M. (January, 2010). A population-based, quasi-experimental investigation on the impact of prenatal maternal stress on fetal, infant, and adult health and psychopathology, Project presented at Indiana Clinical and Translational Sciences Institute Trainee Meeting, Indianapolis, IN.
25. **Class, Q. A.,** D'Onofrio, B. M., Langstrom, N., & Lichtenstein, P. (May, 2009). Early postnatal outcomes of prenatal maternal stress: The importance of timing, Paper presented at the University of California, Irvine.
26. **Class, Q. A.,** D'Onofrio, B. M., Langstrom, N., & Lichtenstein, P. (May, 2009). Timing of maternal stress during pregnancy differentially predicts gestational age at birth, Poster session presented at the Association for Psychological Science Conference, San Francisco, CA.
27. **Class, Q. A.,** D'Onofrio, B. M., Langstrom, N., & Lichtenstein, P. (April, 2009). Prenatal maternal stress predicts gestational age at birth: The importance of timing, Paper presented at Indiana University, Psychological and Brain Sciences Developmental Seminar, Bloomington, IN.
28. **Class, Q. A.,** D'Onofrio, B. M., Ganiban, J., Spotts, E., Lichtenstein, P., Reiss, D., & Neiderhiser, J. (May, 2008). The impact of parental depression on offspring self-concept, Paper presented at the Association for Psychological Science Conference, Chicago, IL.
29. **Class, Q. A.,** Gierczak, M., Pattillo, C., Davis, E., & Sandman, C. A., (2007, February). Exposure to maternal and placental peptides, Paper presented at the Winter Neuropeptide Conference, Breckinridge, CO.
30. **Class, Q. A.,** Gierczak, M., Pattillo, C., Sandman, C. A., & Davis, E. (2006, March). Correlations between maternal salivary cortisol and fetal heart rate. Poster session presented at the annual Gatlinburg Conference on Research and Theory of Intellectual and Developmental Disabilities, San Diego, CA.
31. **Class, Q. A.,** Patterson, J. V., Gierczak, M., & Sandman, C. A., Glynn, L. M. (2006, October). The influence of parity on neurological functioning. Poster session presented at the annual conference of the Society of Psychophysiological Research, Vancouver, Canada.
32. **Class, Q. A.,** & Polich, J. (2006, March). Affective visual stimuli (IAPS) and ERPs: Valence effects and stimulus perceptability. Poster session presented at the annual conference of the Cognitive Neuroscience Society, San Francisco, CA.
33. **Class, Q. A.,** & Polich, J. (2005, June). Affective visual stimuli (IAPS) and ERPs: Valence effects and stimulus perceptability. Paper presented at the annual meeting of the UC San Diego Psychology Honors Program, La Jolla, CA.

RESEARCH EXPERIENCE

2007-2014 Developmental Psychopathology Lab

IU, Department of Psychology and Brain Sciences
Title: Graduate Student
Focus: Examined early risk factors for adverse birth outcomes, infant mortality, and psychological and physical mortality and morbidity throughout the lifespan using genetically-informed, longitudinal designs including sibling-comparison models, Children-of-Twins models, and survival analyses.
Advisor: Brian M. D'Onofrio, Ph.D.

2009-2014 Postpartum Depression fMRI research
IU, Kinsey Institute
Title: Clinical Researcher Coordinator
Focus: A functional magnetic resonance imaging (fMRI) study of brain processing in depressed and non-depressed postpartum and nulliparous women with placebo-controlled investigation of an oxytocin nasal spray intervention. Performed psychological diagnostic evaluations, performed statistical analyses, disseminated research findings through publication and oral presentation, trained undergraduate and junior-level graduate students.
Advisor: Julia Heiman, Ph.D.

2005-2007 Women and Children's Health and Well-being Project
University of California, Irvine (UCI), Department of Psychiatry and Human Behavior
Title: Clinical Research Coordinator
Focus: Investigated the impact of maternal stress on fetal and infant development, interviewed pregnant and postpartum women, administered Bayley's assessments on infants, analyzed fetal heart rate data, and disseminated research findings through publication and oral presentation.
Advisors: Curt A. Sandman, Ph.D. and Laura M. Glynn, Ph.D.

2004-2005 Cognitive Electrophysiology Laboratory
The Scripps Research Institute, Molecular and Integrative Neurosciences
Title: Honors Student and Research Technician
Focus: Investigated the neural correlates of emotional processing, tested participants using EEG equipment, analyzed data, and disseminated research findings through publication and oral presentation.
Advisor: John Polich, Ph.D.

TEACHING EXPERIENCE

UNDERGRADUATE COURSE INSTRUCTOR

2010 Prenatal Development and Theory, IU Bloomington
Constructed and lead semester-long, 1-credit course to an honors undergraduate student

2009 Methods in Experimental Psychology, IU Bloomington
Taught formal, semester-long course to 40 undergraduate students

2005 Statistics, Undergraduate Section Teaching Assistant, UCSD

Taught 2 40-student lab sections, provided test preparation lectures, graded tests

UNDERGRADUATE GUEST LECTURER

2013 "Birth and the Family: Breastfeeding", IU Bloomington
2013 "Developmental Psychopathology: The perinatal period", IU Bloomington
2010, 2011 "Abnormal Psychology and Stress", IU Bloomington
2010 "Health Behavior Change: Smoking Cessation", IU Bloomington
2009 **"**The Treatment of Anxiety Disorders", IU Bloomington

ELEMENTARY TEACHING

2003 Special Education Teaching Assistant, Dublin, Ireland
Provided afterschool homework and social support to at-risk children (aged 4-10 years)

CLINICAL EXPERIENCE

CLINICAL TRAINING

2015 Adult Outpatient Psychiatry Clinic, IU Neuroscience Center; Advance Heart and Lung Care Clinic, Methodist Hospital; Simon Cancer Center Multidisciplinary Clinic, Indianapolis, IN
Title: Individual Therapist
Focus: Conduct clinical interviews and diagnostic assessments, provide individual and group psychotherapy using cognitive-behavioral and acceptance and commitment strategies in general, cardiac, and cancer populations, receive individual and group supervision.
Supervisor: Yelena Chernyak, Ph.D.

2015 Child and Adolescent Inpatient Services, Larue Carter Memorial Hospital, Indianapolis, IN
Title: Individual Therapist
Focus: Use evidence-based therapies in children aged 7 to 17 years old with severe psychological, behavioral, and trauma-based disorders in individual and group settings. Participate on multidisciplinary treatment team.
Supervisor: Melissa Butler, Ph.D.

*2*015 Adult Inpatient Services Program, Larue Carter Memorial Hospital, Indianapolis, IN
Title: Individual Therapist
Focus: Use dialectical behavior-based, metacognitive, illness management and recovery, and social skills training therapy to treat inpatient psychotic spectrum, schizophrenic, major mood, forensic, and personality disordered patients often with comorbid substance use disorders and intellectual disabilities in individual and group settings. Supervise medical students and psychology graduate students.
Supervisor: Jennifer Vohs, Ph.D.

2015 Adult Neuropsychology Clinic, Indiana University Neuroscience Center, Indianapolis, IN
Title: Neuropsychology Intern

Focus: Administer, score, and interpret tests for neuropsychological evaluations, perform clinical interview and feedback to patients and families, engage in 90 minute case conference and a variety of didactic experiences
Supervisor: Daniel Rexroth, Ph.D.

2014 Pediatric Psychiatry, Riley Hospital for Children, Indianapolis, IN
Title: Pediatric Consult-Liaison Psychology Intern
Focus: Provide inpatient mental health services hospital-wide. Services include diagnostic assessment, pain management, behavioral interventions, family conflict, biofeedback, coping with chronic or terminal illness, feeding issues, pre- and post-transplant evaluations, Somatoform disorders, altered mental status and psychosis, and overdose/ingestion cases. Participate in the multidisciplinary team and work with medical staff. Supervise medical students.
Supervisor: Amy E. Williams, Ph.D.

2014 Child Mood Clinic, Riley Hospital for Children, Indianapolis, IN
Title: Individual and Co-Therapist
Focus: Individual assessment and therapy using evidence-based practice following CBT, IPT, Parent Behavior Training, and Family Systems approaches for children and adolescents with mood and anxiety disorders including OCD with frequent co-morbidity with ADHD and ODD.
Supervisor: Ann Lagges, Ph.D.

2012-2014 Cognitive Behavioral Therapy Research and Training Clinic, IU Bloomington
Title: Individual Therapist
Focus: Conducted diagnostic intake assessments using SCID-I and wrote comprehensive, integrated reports. Utilized CBT, BA, and mindfulness for depression and dysthymia. CBT for social anxiety, panic disorder, generalized anxiety, and obsessive-compulsive disorder. Participated in individual and group supervision in a principles-based approach to CBT. Trained to use the CTRS for improving clinical skills.
Supervisor: Cara C. Lewis, Ph.D.

2012 Psychosocial Rehabilitation and Recovery Center, Roudebush VA Hospital, Indianapolis, IN
Title: Individual Therapist
Focus: Used integrative metacognitive therapy in group and individual therapy with severely mentally ill veterans. Group therapy included process, social skills, stress management, and addiction recovery.
Supervisor: Paul Lysaker, Ph.D.

2011-2012 Alternative Alcohol and Marijuana Intervention Program Practicum, IU Office of Student Affairs, Bloomington
Title: Individual Therapist
Focus: Conducted brief motivational interviewing and behavioral intervention strategies for undergraduate students struggling with alcohol and drug use and associated negative academic and legal ramifications.
Supervisor: Walter Keller, Ph.D.

2011 Adult Outpatient Clinic, IU Hospital, Indianapolis
Title: Individual Therapist
Focus: Performed semi-structured intake assessments. Conducted CBT and BA for anxiety, depression, and OCD.
Supervisor: Jeffrey D. Lightfoot, Ph.D.

2010 Child and Adolescent Psychiatry Outpatient Center: Psychological Testing and Measurement Specialty Clinic, Riley Hospital for Children, Indianapolis
Title: Individual Therapist
Focus: Conducted child, adolescent, and adult neuropsychological assessments. Trained in testing, administration/scoring, behavioral observations, and preliminary case formulations. Trained in administering Beery-Buktenica Developmental Test of Visual-Motor Integration, California Verbal Learning Test, Comprehensive Test of Phonological Processing, D-KEFS Trail Making Test, Gray Oral Reading Test, Kaufman Brief Intelligence Test, Peabody Picture Vocabulary Test, Stroop Color-Word test, Test of Reading Comprehension, Test of Word Reading Efficiency, Thematic Apperception Test, Wechsler Adult Intelligence Scale, Wechsler Intelligence Scale for Children, Wide Range Assessment of Memory and Learning, Woodcock-Johnson Test of Achievement.
Supervisor: William G. Kronenberger, Ph.D.

2010 Sensorimotor Assessment and Training Project, IU Bloomington
Title: Clinical technician
Focus: Administered, scored, and interpreted Beery-Buktenica Developmental Tests of Visual-Motor Integration, 6th edition, on 7-9 year old children at a local elementary school as a contributing research therapist.
Supervisor: Geoff Bingham, Ph.D.

2009-2011 Postpartum Psychopathology Project, IU Kinsey Institute, Bloomington
Title: Individual Therapist/Clinical Consultant
Focus: Administered semi-structured postpartum depression evaluations as a co-research therapist (alongside psychiatrist) with community members participating in research.
Supervisor: Johan Verhulst, M.D. & Julia Heiman, Ph.D.

2009-2010 Evidence Based Behavioral Medicine Practicum, IU Bloomington
Title: Individual Therapist
Focus: Provided individual therapy for depression, anxiety, and chronic headaches using an evidence-based, integrative approach based on CBT principles.
Supervisor: Barbara Walker, Ph.D.

2009-2010 Volunteers in Medicine, Bloomington, IN
Title: Individual Therapist
Focus: Provided individual therapy focused on behavioral health intervention strategies, crisis management, and support building for people suffering from diabetes, chronic pain, depression, anxiety, and systematic consequences of low socioeconomic status. Co-facilitated smoking cessation, and pain management group.
Supervisor: Barbara Walker, Ph.D.

2008-2012 Parent Behavior Training Practicum, IU Bloomington
Title: Individual and Co-Therapist
Focus: Conducted diagnostic assessments using semi-structured interview and wrote integrated reports for each intake. Provided empirically-supported Fleischman and colleagues' family-based parent behavior training protocol for children with ODD. Conducted school and home observations as needed.
Supervisor: John E. Bates, Ph.D.

CLINICAL SUPERVISION

2015 Supervisor, Adult Outpatient, Indiana University Neuroscience Center
2015 Supervisor, Adult Inpatient, Larue Carter Memorial Hospital
2014 Supervisor (medical students), Pediatric Consult-Liaison, Riley Hospital for Children
2013-2014 Peer Supervisor, Evidence-Based Clinical Supervision Course, IU Bloomington
2012-2014 Peer Supervisor, Cognitive Behavioral Therapies for Anxiety and Depression Practicum, IU Bloomington
2011-2013 Peer Supervisor, Evidence Based Psychosocial Intervention Consultation Period for Advanced Clinical Doctoral Students Enrolled in External Practica, IU Bloomington
2012 Peer Supervisor, Alternative Alcohol Intervention Program Practicum, IU Office of Student Affairs, Bloomington
2010-2012 Peer Supervisor, Parent Behavior Training Clinic, IU Bloomington

PROFESSIONAL DEVELOPMENT

STATISTICAL TRAINING

2011 Introduction to Structural Equation Modeling (R), University of Virginia, VA
2008 Survival Analysis using SAS, Statistical Horizons Training, Atlanta, GA
2006 Statistical Analysis System (SAS), UCI Statistical Consulting, Irvine, CA

FORMAL ETHICAL TRAINING

2012 Responsible Collaboration & Authorship Workshop
2011 Responsible Conduct of Research Graded Course (A)
2011 Panel Member, "Ethical Data Management", IU Research Ethics, Education, and Policy

CLINICAL TRAINING WORKSHOPS

2011 Structured Clinical Interview DSM-IV-TR Axis I Disorders, Cara Lewis, Ph.D.
2009 Smoking Cessation, Barbara Walker, Ph.D.
2007 Child Inclusive Dispute Resolution, Jennifer McIntosh, Ph.D.
2008 Cognitive Behavioral Therapy for Pain, Beverly Thorn, Ph.D.

AD-HOC REVIEWER (FIRST YEAR AS REVIEWER)

2015 American Journal of Epidemiology
2015 The American Journal of Psychiatry
2015 The American Journal of Managed Care
2014 Pediatrics
2014 Schizophrenia Bulletin
2013 Neuroscience and Biobehavioral Reviews

2013 Journal of Abnormal Child Psychology
2012 Journal of Adolescent Health
2012 Psychological Medicine
2011 Frontiers in Developmental Psychology

COMMUNITY AND UNIVERSITY SERVICE AND CERTIFICATIONS

2014 Crisis Prevention Intervention, Nonviolent Intervention, Doug Gaebler, LCSW
2014 Basic Life Service CPR Certification, American Heart Association
2012 IU Graduate and Professional Student Organization (GPSO), Travel Grant Reviewer
2011-2012 GPSO Psychology and Brain Sciences Representative
2011-2012 GPSO Health Benefits Committee Member
2011 Girl Scouts of America: Brownie Math and Science Career Day
2009-2010 Volunteers in Medicine, Community clinic for the uninsured
2008 Trauma Intervention Specialist, Orange County, CA Chapter
2006-2008 Student Health Advocate, Health and Wellness Clinic, UCSD

PRESS

2013 National Abandoned Infants Assistance Resource Center website, UC Berkeley

SOCIETY MEMBERSHIP (MEMBER SINCE)

2014 Indiana Psychological Association
2011 Society for Research in Child Development
2011 Association for Contextual Behavioral Science
2010 Society for the Teaching of Psychology
2010 Behavioral Genetics Association
2009 Society for Clinical and Translational Science
2009 Society for a Science of Clinical Psychology
2008 Association for Psychological Science
2002 National Society for Collegiate Scholars